Appendix 7.1: Socio Economic Impact Statement

Aughinish Alumina Ltd

Socio-Economic Impact Statement

KPMG

September 2021

This report contains 9 pages

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Aughinish Alumina Ltd
Socio-Economic Impact Statement
KPMG Future Analytics
August 2021

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Aughinish Alumina Ltd
Socio-Economic Impact Statement
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1 Introduction

This report outlines the findings of a detailed economic and socio-economic assessment of the current and potential future impact of Aughinish Alumina Ltd (Aughinish). Aughinish is an alumina refinery which has been located in County Limerick since 1983. The refinery site is a major process manufacturing facility covering 601 hectares, directly employing 482 staff with an additional 385 on-site contractor personnel. Aughinish is the only producer of alumina in Ireland and the largest producer of alumina in Europe. It provides ~30% of the EU's alumina, much of which is used for aluminium in everything from food packaging to food preparation, from medicines to medical devices, and power lines to mobile phones. Aughinish is among the top 5 alumina refineries in the world in terms of minimum carbon emissions.

The facility plays a significant role in the Mid-West and Irish economy. This report examines the impacts of the facility at both national and regional levels across a number of core themes: 1. Economy, 2. Demographic Profile and Spatial Impacts (including commuting patterns across the region, and 3. Infrastructural and industrial impacts.

1.1 Key Summary Insights

- Aughinish's operational activities and those of its supply chain generate €130 million in value for the Irish economy. Each €1 spent by Aughinish results in an additional €0.40 spend by suppliers.
- Aughinish's capital investment activities and the additional spend of suppliers generates ~€10 million in value for the Irish economy and, in particular, for the Mid-West.
- In 2021, capital investment will be more than 60% higher than in 2020 and will grow further as Aughinish's own contribution to decarbonisation, waste reduction, community amenities and other environmental projects increases over the coming years.
- Aughinish supports ~965 jobs through its spend on suppliers and across its value chain: ~840 jobs arising from operational activities and ~125 jobs arising from its capital activities.
- Through its operational activities, Aughinish supports the payment of ~€50 million in labour income across its supply chain. Additionally, labour income arising from capital activities is ~€6 million.
- The Aughinish CHP Plant (the largest in Ireland) produces 160 megawatts (MW) of electricity, using 45 MW to power the refinery and exporting 115MW of power to the national grid; enough to power 200,000 households.
- In 2020, the plant spent a total of €373 million on operational activities and €18 million on capital investment activities – significant sums in the context of the Mid-West economy.
- Aughinish's natural deep-water port is the third largest nationally in total tonnage after Dublin and Cork.

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2 Economic and spatial impacts

- Aughinish Alumina Limited (Aughinish) is an alumina refinery located in County Limerick since 1983. The refinery site is a major process manufacturing facility covering 601 hectares, directly employing 482 staff with an additional 385 on site contractor personnel.

- In 2020, the plant spent a total of €373 million on operational activities and €18 million on capital investment activities – significant sums in the context of the Mid-West economy. In the same year Aughinish spent over €35.4 million towards direct employee salaries with additional spend of €11.2 million on benefits packages.

- Aughinish's expenditure creates additional labour incomes throughout its value chain totalling €56 million, with ~90% of this income generated as a result of the facility's operational activities.

- Total labour tax contributions from activities at Aughinish are estimated to be ~€35 million.

    - Contributions through employer PRSI is estimated to sum to more than €10.5 million, with employee PRSI summing to circa €4.0 million.

    - Income tax paid by direct employees and employees within the supply chain is estimated to be greater than €17.5 million, with Universal Social Charge (USC) payments estimated to be greater than €3.4 million

- Separate to the onsite contractor personnel the total number of jobs supported in its supply chain is estimated to be 965 jobs of which 840 (87%) are supported as a result of Aughinish's operational activities and 125 arise from capital activities at Aughinish.

- Salaries of direct Aughinish employees are on average 51% higher than salaries in the wider economy, meaning the refinery's contribution to labour income is relatively stronger than that of the wider population.

- Aughinish also provides premium benefit packages with base salaries across all industries including pension package and health insurance.

- Amongst the craft and process operators' group, the average salary at Aughinish is €63,363, €16,259 higher when compared to the national average salary of €47,000.

- In the Support group, the average salary at Aughinish is €62,844, €30,773 higher than the average salary for this group nationally of 32,071.

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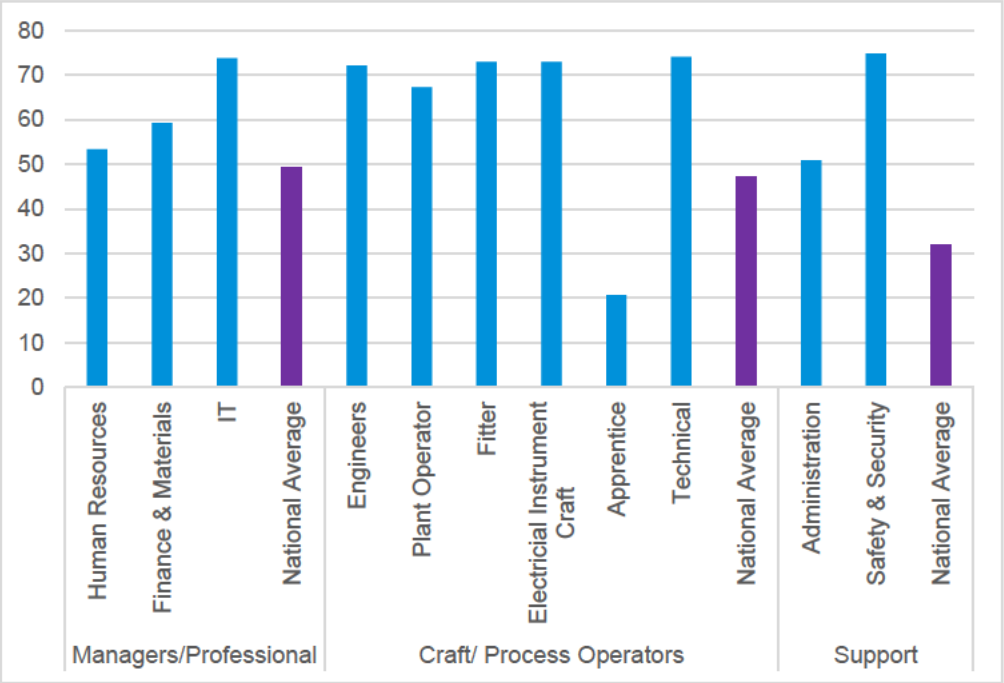


Figure 1. Comparative Average Salary Range (€'000)

- The facility is estimated to generate ~€140 million for the Irish economy (GVA). Out of this amount, 70% are direct impacts arising from Aughinish's spend, with 30% arising from suppliers spend.
- Aughinish contributes ~€4 million in local contributions to Limerick City, County Council and Port Authority. This significant contribution supports local employment, local services, and investments in communities.
- The facility has the potential to continue to operate and implement advanced technologies, subject to approvals.
- A total of 10.41% of Aughinish direct employees live within a 15-minute commute from the facility, 44.49% undertake a commute of 30 minutes, while 31.63% of employees noted a 45-minute commute. The remaining 13.47% undertake a commute between 60 to 75 minutes to the facility.

Table 1 Commuting times of Direct Employees and Contractor Personnel

Commute Times	< 15 minutes	< 30 minutes	< 45 minutes	Other
Direct Aughinish Employees	10.41%	44.49%	31.63%	13.47%
Onsite Contractor Personnel	8.55%	40.79%	23.68%	26.97%

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- Co. Limerick is the preferred residence for Aughinish direct employees with 74%, Co Kerry is the second largest with 16%, while Co. Clare recorded the third largest place of residence with 4%. The remaining 5% of direct employees travel from Counties Tipperary, Cork, and Offaly.

- Over 8.55% of onsite contractor personnel travel within 15 minutes to the facility. The largest commute time is 30 minutes with 40.79%. The second largest recorded time was 45-minutes with 23.68%. The remaining 26.97% of onsite contractor personnel undertake a commute between 60 to 75 minutes.

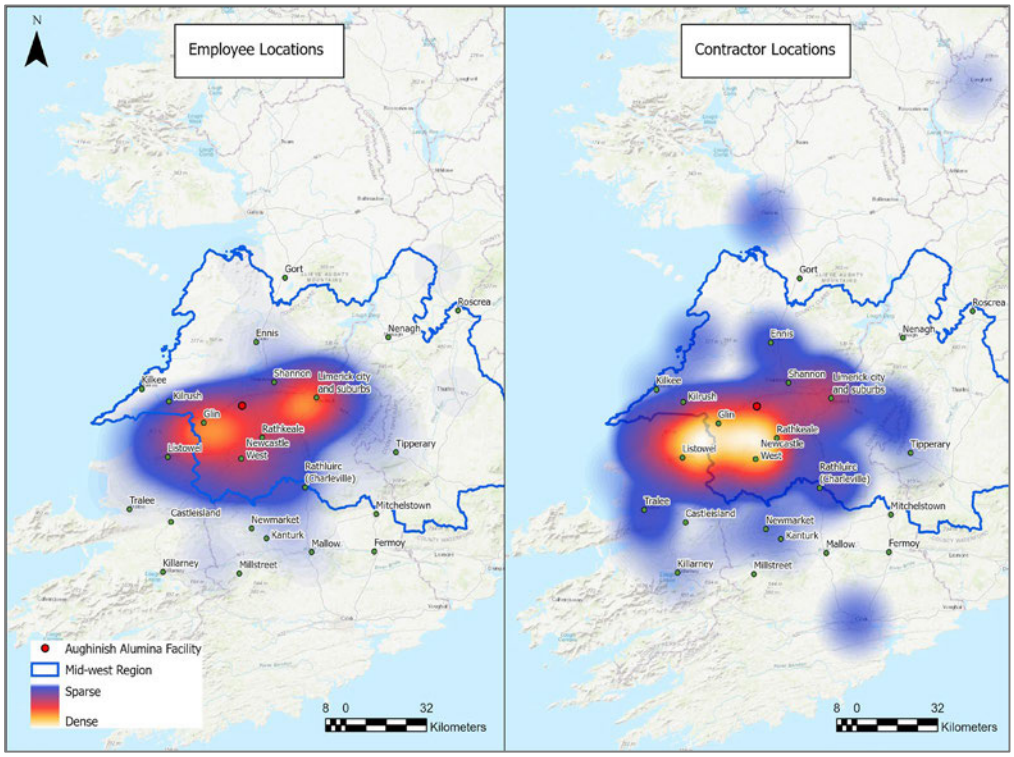


Figure 2. Employee & Contractor Locations

- The counties of residence among onsite contractor personnel follows a similar trend of direct employees with 56% residing in Co. Limerick while 30% reside in Co. Kerry, with a further 13.5% on-site contractor personnel residing in Clare, Tipperary, and others.

- The main urban settlements in which direct employees reside are Limerick City and the village of Glin, while on-site contractor personnel mostly reside in the settlements of Rathkeale, Listowel, Glin and Newcastle West.

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3 Demographics

- Aughinish currently employs 482 staff.
- The greatest number of employees are plant operatives (177, 41% of total). A total of 90 fitters and 49 technical staff complete the second and third largest groupings, respectively accounting for 19% and 10% of the entire workforce – together these job categories make up 70% of all employees at Aughinish Alumina.
- The facility's workforce has an average age of 45, with 26% of all staff aged 60 or more, 40% of the workforce is aged between 30 and 45 years old. The average age of the onsite contractor personnel is 42 years old.

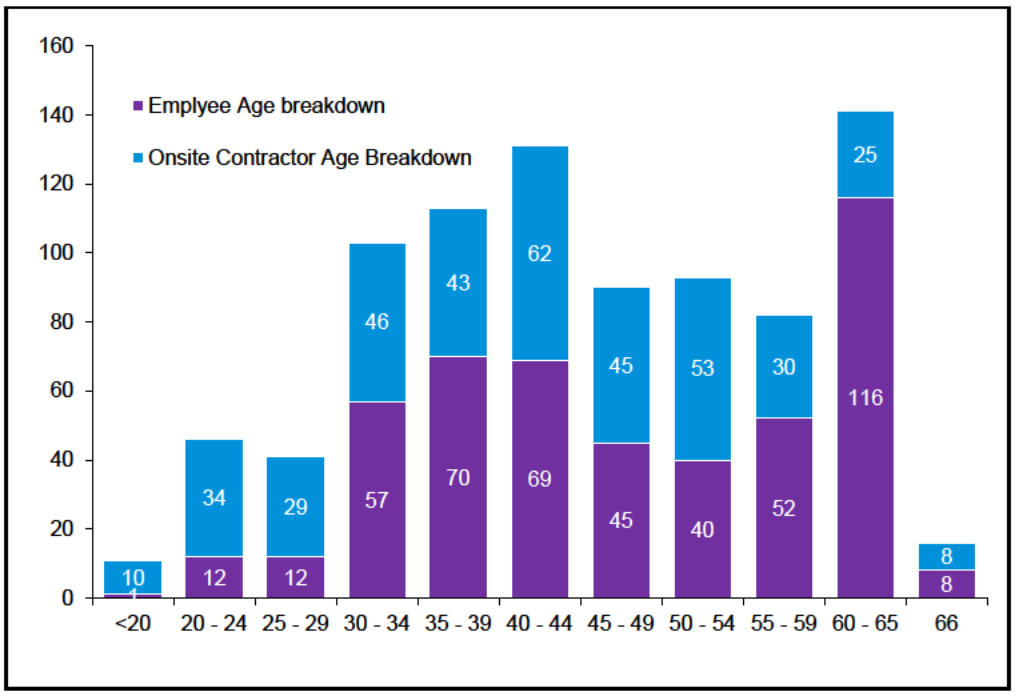


Figure 3. Demographic profile of staff and on-site contractors, number of members

- Since 1983 Aughinish has provided continuous long-term employment to the region. Between 2021 and 2025, 125 of the Aughinish's direct employees will retire and all of these positions will be refilled.
- Direct employees of Aughinish each receive a minimum of 40 hours training per annum. with funding provided by Aughinish for further education and post-graduate training.
- Development of potential future leaders for the organisation includes a BA Management programme at University of Limerick.
- Aughinish participates in academic research through its long-standing relationship with UL while also collaborating with a further 12 international research institutions throughout the world.

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4 Infrastructural & Industrial impacts

- Aughinish is the only producer of alumina in Ireland and the largest producer in Europe, it provides 30 per cent of the EU's alumina, much of which is used for aluminium in a multitude of applications.
- Aluminium is used in everything from food packaging to food preparation, from medicines to medical devices, and power lines to mobile phones.
- Aughinish is among the top 5 alumina refineries in the world in terms of minimum carbon emissions.
- Aughinish's natural deep-water terminal is the third largest nationally in total tonnage throughput (after Dublin and Cork). Since 2015, the port has handled 21% of all EU Dry Bulk goods transported through Irish ports making it the second busiest nationally after Dublin.

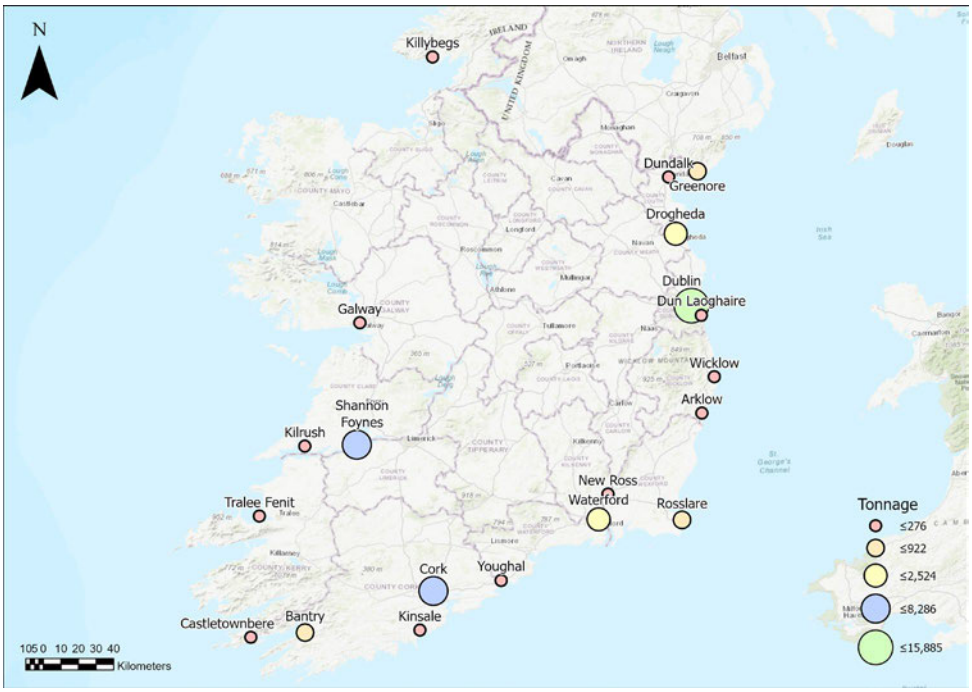


Figure 4. Tonnage of Goods Handled to Other EU Ports in 2020

- In 2014 two new Gas Boilers were installed at Aughinish, completing the move to 100% natural gas and away from fuel oil.
- The switch to natural gas enabled Aughinish to significantly improve its environmental performance.
- Aughinish consumes circa 10% of natural gas in the Irish market and up to 15% during summer months. This large share contributes ~10% to the gas network transportation revenues in Ireland helping to reduce the tariff burden on all other network users.

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- The Aughinish CHP Plant (the largest in Ireland) produces 160 megawatts (MW) of electricity, using 45 MW to power the refinery and exporting 115MW of power to the national grid; enough to power 200,000 households.

- Outside of renewable electricity, Aughinish's CHP plant is the lowest carbon emitting electricity producer in Ireland. Electricity generated by Aughinish CHP has a carbon intensity of 0.240t carbon/MW.h which is lower than the current national grid average of 0.324t carbon/MW.h

- Aughinish has participated in the EU Emissions Trading System since it started in 2005 and supports the reinforcement of Ireland's energy security needs by researching feasible alternatives to natural gas and investing in energy efficiency measures such as CHP generation.

- Aughinish contributes significantly to the natural environment surrounding the facility.

- Aughinish is a leading facility, operating in accordance with international standards:

  - **ISO 14001** (environmental management standard)
  - **ISO 9001** (quality management standard)
  - **ISO50001** (international energy standard
  - **ISRS** (health and safety management standard)

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Appendix 7.2: External Emergency Plan

8 ADDENDA

Comhairle Cathrach
& Contae **Luimnigh**

Limerick City
& County Council

External Emergency Plan

For

Bauxite Residue Disposal Area

Aughinish Alumina Ltd.
Askeaton
Co. Limerick

Title:	**AAL BRDA EXTERNAL EMERGENCY PLAN**
Version:	**2.0**
Date:	**2nd August 2019**
Status:	**Final**
Prepared By:	**Limerick City & County Council**

External Emergency Plan – BRDA, Aughinish Alumina Ltd.

This External Emergency Plan for the Bauxite Residue Disposal Area, Aughinish Alumina Ltd., Aughinish West, Askeaton, Co. Limerick has been developed and approved by Limerick City & County Council in accordance with the requirements of the Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009).

C. Doherty

Limerick City & County Council

Date: 8th Aug 2019

RECORD OF ISSUES AND AMENDMENTS

NOTE:
Any changes made to the Aughinish Alumina Ltd. facility regarding site layout, structure of plant, operating procedures or change/quantity of dangerous substances stored on site, that may have an impact on this External Emergency Plan, shall be notified to Limerick City & County Council.

External Emergency Plan Working Group (EEPWG)		
Names	**Title**	**Organisation**
Stephane Duclot	Senior Manager	Limerick City & County Council
Gerrard Doherty	Senior Executive Engineer, Environment	Limerick City & County Council
Ursula Ahern	A/ Executive Scientist	Limerick City & County Council

Documents used in the preparation of this External Emergency Plan	
1.	Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009)
2.	EPA Guidance on the Waste Management (Management of Waste from the Extractive Industries) Regulations 2009 – published June 2012
3.	A Framework for Major Emergency Management – Guidance Document 10: *A Guide for PRA Local Competent Authorities under S.I No.209 of 2015 European Communities (Control of Major Accident Hazards Involving Dangerous Substances) Regulations 2015- October 2015.*
4.	*RUSAL Aughinish Emergency Procedures – BRDA Containment Failure – Iss1Rev2 of April 2013*
5.	RUSAL Aughinish Emergency Response Plan – March 2013
6.	Risk Assessment and Break-Out Study for the Bauxite Residue Disposal Area at Aughinish Alumina – March 2013
7.	Aughinish Alumina Ltd. 2005 BRDA Extension Environmental Impact Statement.
8.	Limerick City and County Council's Major Emergency Plan

Record of Issues and Amendments			
Version No.	**Date**	**Section Amended**	**Amended By**
Issue 1.0	June 2013	Original External Emergency Plan.	Limerick County Council
Issue 1.1	July 2013	Comments from HSE and EPA incorporated	Limerick County Council
Issue 1.2	September 2013	Final version following Public Consultation.	Limerick County Council
Issue 1.3	April 2015	Review following Testing of Plan	Limerick City & County Council
Issue 1.4	January 2016	Final Review following Testing	Limerick City & County Council
Issue 1.5	February 2019	Draft for Review	Limerick City &

			County Council
Issue 2.0	August 2019	Final Review following Testing	Limerick City & County Council

Exercise and Review Record		
Date	**Type of Exercise**	**Comments**
06 March 2015	Table-Top Exercise	
6th March 2019	Table-Top Exercise	

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DISTRIBUTION LIST

A copy of the reviewed External Emergency Plan shall be distributed to the following agencies.

Limerick City & County Council	Chief Executive
An Garda Síochána	Chief Superintendent
Health Service Executive	Regional Emergency Management Office
Aughinish Alumina Ltd.	Environmental Manager
Health and Safety Authority	Manager
Environmental Protection Agency	Inspector (Cork Office)
Munster Regional Communications Centre	Senior Executive Emergency Communications Officer
Shannon Foynes Port Authority	Harbour Master
National Parks and Wildlife Service (NPWS)	Regional Manager
Office of Public Works (OPW)	Assistant Chief Engineer, Templemungret

Individual agencies should circulate sufficient copies for distribution to the relevant personnel within their organisation. As required, the Local Competent Authorities will update the plan and redistribute to the above list.

INTRODUCTION

This is the External Emergency Plan for:

BAUXITE RESIDUE DISPOSAL AREA (BRDA)
AUGHINISH ALUMINA LTD.
AUGHINISH WEST
ASKEATON,
CO. LIMERICK.

Aughinish Alumina Ltd. is an alumina refinery situated on Aughinish Island on the south side of the Shannon estuary near Foynes, 20 miles downstream from Limerick City.
The plant produces over 1.8 million tonnes of alumina (Al_2O_3) per annum by processing bauxite ore, a reddish brown earth, using the Bayer process. Alumina is a fine white granular powder, which is exported to aluminium smelters for processing into aluminium metal.

The Bayer Method results in the production of bauxite residues (primarily non-hazardous but with a 1.0 -1.5% hazardous constituent) which is deposited in the lined Bauxite Residue Disposal Area within the facility boundary. The process yields approximately 0.3 tonnes of waste for disposal for each tonne of bauxite processed. The BRDA comprises 2 separate phases. Phase 1 comprises 104 ha and is substantially filled. Phase 2 comprises 78 ha and is currently being filled. It is estimated that there is 12 years of capacity within the constructed BRDA (to 2031).

The EPA has classified the Bauxite Residue Disposal Area at Aughinish Alumina Ltd. as a Category A Waste Facility as defined in Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009).

Golder Associates prepared a Risk Assessment and Break-out study of the BRDA in 2012, on behalf of Aughinish Alumina Ltd. This assessment concluded that the probability of a breach or failure of BRDA containment is very unlikely to negligible. Aughinish Alumina Ltd. Emergency Response Procedure considers two worst-case scenarios in which a breach or failure of BRDA containment may occur:

1. A release of alkaline waste water in the Perimeter Interceptor Channel over the top of the Outer Perimeter Embankment Wall of the Phase 1 BRDA

2. A release of red mud slurry into the Perimeter Interceptor Channel and over the top of the Outer Perimeter Embankment Wall of the Phase 1 BRDA

This External Emergency Plan has been prepared by Limerick City and County Council, in accordance with the requirements of the Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009).

The relevant Authorities in respect of this External Emergency Plan are:

- Environmental Protection Agency (in respect of IE (Industrial Emissions) Licencing & Competent Authority under SI 566 of 2009)
- Limerick City & County Council (responsible for preparation of External Emergency Plan as outlined in SI 566 of 2009 and Principal Response Agency)
- An Garda Síochána (Limerick Division) (Principal Response Agency)
- Health Service Executive (West) (Principal Response Agency)

The objectives of this External Emergency Plan are to prepare for:

- Containment and control of major accidents and other incidents so as to minimise their effects and in particular to limit damage to human health and the environment;
- Implementation of measures necessary to protect human health and the environment from the effects of major accidents and other incidents;
- Communication of the necessary information to the public and to the relevant services or authorities in the area;
- Provision for the rehabilitation, restoration and clean-up of the environment following a major accident.

This External Emergency Plan may also be read and implemented in conjunction with:-

- RUSAL Aughinish Emergency Response Plan
- RUSAL Aughinish Emergency Procedures – BRDA Containment Failure
- The Major Emergency Plans of:
  - Limerick City & County Council
  - An Garda Síochána (Limerick)
  - Health Service Executive (West)

In addition to other sources of information, responding organisations / agencies should refer to this External Emergency Plan when responding to a major incident at BRDA Facility, Aughinish Alumina Ltd.

NOTE:

This External Emergency Plan is a specific Sub-Plan of the Major Emergency Plan of Limerick City & County Council.

The activation of this External Emergency Plan may not warrant a declaration of a Major Emergency and the activation of the procedures contained within the Major Emergency Plan. A decision on whether or not the emergency requires the activation of the Major Emergency Plan will reside with the authorized officer of Limerick City and County Council.

A *"Framework for Major Emergency Management"* sets out the co-ordination arrangements and terminology for use in the event of a Major Emergency (e.g. Lead Agency concept, Information Management System, On-Site Coordinator, Controller of Operations and Media Liaison Officers etc.).

It is also appropriate that Framework arrangements and terminology are used in emergency situations where a Major Emergency has not been declared. These arrangements have been incorporated into this External Emergency Plan where necessary.

1.0 ACTIVATION AND STAND DOWN

1.1 When will this Plan be activated?

This Plan will be activated without delay when:

- A major accident occurs[1]; or
- An uncontrolled event occurs which could be reasonably expected to lead to a major accident.

A major accident[2] is an occurrence on site in the course of an operation involving the management of extractive waste in any establishment covered by Directive 2006/21/EC , leading to a serious danger to human health and/or the environment, whether immediately or over time, on-site or off-site;

1.2 Responsibility for activating this Plan

The following personnel from **Aughinish Alumina Ltd.** may request the activation of this plan:

Name	Position	Contact Number	Mobile Number
Louise Clune	Environmental Manager	061-604243	[redacted]
Ciaran Kelleher	Adminstration Manager		[redacted]
John Horan	Hydrate Plant Manager		[redacted]
Donie McEnery	BRDA Manager		[redacted]

The following personnel from Limerick City & County Council are authorized to activate this plan:

Name	Position	Contact Number	Mobile Number
Kieran Lehane	Director of Services	061-557387	087-2693037
Stephane Duclot	Senior Manager	061-556445	087-2033317
Gerrard Doherty	Senior Executive Engineer	061-556245	087-2289955

[1] The term 'major accident' is used to reflect its usage and definition in the Regulations – Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009) Note that a 'major accident at a Category A Waste Facility may NOT NECESSARILY be of sufficient impact on the capabilities of the emergency services to require the declaration of a Major Emergency under the Framework. The Site Operator should NOT use the METHANE format.

[2] "major accident" defined in Waste Management (Management of Waste from the Extractive Industries) Regulations, 2009 (S.I. 566 of 2009);

1.3 How this plan will be activated?

An authorised member of Aughinish Alumina Ltd. will make a telephone call to the following:

	Limerick City & County Council
1.	Limerick City & County Council Planning & Environmental Services Section: 061-556000
2.	Limerick City & County Council Out of Hours Emergency Number: 061-417833

The following personnel will then be contacted to establish the status of the incident:

	Planning & Environmental Services Section
1.	Kieran Lehane, Director of Services
2.	Stephane Duclot, Senior Manager
3.	Gerrard Doherty, Senior Executive Engineer

The above personnel of Limerick City & County Council will contact, via 999/122, the following principal response agencies, **as required**:

	Agency
1.	Limerick City & County Council Emergency Services via the Munster Regional Communication Centre.
2.	H.S.E., National Ambulance Service, National Emergency Operations Centre (NEOC), Rivers Building, Tallaght, Dublin.
3.	An Garda Síochána Divisional HQ, Henry Street, Limerick.

1.4 Information to be provided

When making the activation telephone call, Aughinish Alumina Ltd. must provide the following information to Limerick City & County Council:

- Site Name and Address:
  AUGHINISH ALUMINA LTD., Aughinish West, Askeaton, Co. Limerick.
- The fact that the BRDA at Aughinish Alumina Ltd. is a Category A Facility and that the emergency requires the activation of the External Emergency Plan. Note if the emergency is environmental and/or if there is risk to human health.
- Provide details of the incident using the following **ETHANE** format:

MNEMONIC 'ETHANE' MESSAGE TO DELIVER		
E	Exact Location	Specific building or installation on site
T	Type of Incident	Release of alkaline waste water/red mud slurry in the Perimeter Interceptor Channel and over the top of the Outer Perimeter Embankment Wall of the Phase 1 BRDA.
H	Hazards	Current and potential
A	Access	From which direction to approach
N	Number of casualties	The type/severity
E	Emergency services	Present and required

NOTE:
If it appears to one or more of the Principal Response Agencies that a major accident has occurred or an uncontrolled evnt has occurred which could be reasonably expected to lead to a major accident at Bauxite Residue Disposal Area, Aughinish Alumina Ltd., then Limerick City & County Council should activate this plan as set out above for BRDA, Aughinish Alumina Ltd.

On activation of this plan Limerick City and County Council will implement their key actions as outlined in Section 2.

1.5 Initial Actions of Limerick City and County Council

The Planning & Environmental Services Section of Limerick City and Council shall meet the Site Manager at the pre-determined meeting point, which is the reception/security building at Aughinish Alumina Ltd. The Aughinish Alumina Ltd. Plant Management may change the location of the meeting point on activation of this plan.

The most senior person from Limerick City and County Council shall be the designated Controller of Operations / On-Site Co-ordinator.

1.6 Major Emergency

DEFINITION
A Major Emergency is any event which, usually with little or no warning, causes or threatens death or injury, serious disruption of essential services or damage to property, the environment or infrastructure beyond the normal capabilities of the principal emergency services in the area in which the event occurs, and requires the activation of specific additional procedures and the mobilization of additional resources to ensure an effective, co-coordinated response.

Any one of the three Principal Response Agencies (An Garda Síochána, Health Service Executive and Limerick City & County Council) may declare a major emergency, which

will activate each agencies pre-determined arrangement in response to a major emergency.

1.7 Standing Down of the Plan

Where a **Major Emergency has been declared**, the decision to stand down the incident at the site, and to announce an "All Clear" to the public, will be taken by the On Site Co-ordinator, in consultation with the other Controllers of Operations at the site and the Local Co-ordination Group.

Where a **Major Emergency has NOT been declared**, the decision to stand down this External Emergency Plan and to announce an "All Clear" to the public will be taken by Limerick City & County Council, in consultation with the Environmental Co-ordinator of Aughinish Alumina Ltd.

2.0 KEY ACTIONS

2.1 Aughinish Alumina Ltd.

	KEY ACTIONS – Aughinish Alumina Ltd.
1.	Implement the pre-determined emergency response arrangements as set out in the Internal Emergency Plan (comprising Rusal Aughinish Emergency Response Plan and BRDA Containment Failure – Emergency Procedure).
2.	Contact Limerick City & County Council to prompt the activation of this External Emergency Plan and provide all relevant information provided as per sections 1.3 and 1.4 of this plan. Contact EPA as per Condition 9.3 of AAL's IPPC Licence.
3.	Ensure that a Meeting Point is identified and communicated to the Planning & Environmental Section of Limerick City and County Council.
4.	Ensure the conference room in the on-site co-ordination centre is available along with 4 information boards/flip charts to detail (1) Current Situation (2) Key Issues (3) Strategic aims/priorities (4) Actions
5.	Arrange for the Environmental Manager to meet with the Senior Officers of Limerick City and County Council at the agreed Meeting Point.
6.	Provide all relevant information to the Limerick City and County Council in relation to the incident.
7.	Provide site specific PPE and diphotherine spray to agencies where required. Identify location of drench showers and additional supplementary supplies of PPE / dipotherine on the BRDA road.
8.	Provide a marshalling officer at Rendezvous Point (RVP).
9.	Ensure that there is a co-ordinated public and media response, with Limerick City & County Council, to the emergency as outlined in Section 6.0 of the External Emergency Plan.
10.	If required, establish a Media Briefing Centre in con-junction with Limerick City & County Council.

2.2 Limerick City & County Council

	KEY ACTIONS – LIMERICK CITY & COUNTY COUNCIL
1.	Consider the requirement to declare a Major Emergency as per the Limerick City & County Council Major Emergency Plan.
	If a Major Emergency is NOT declared:
2.	Limerick City & County Council shall mobilise a Controller of Operations who will take command of the response.
3.	Activate the Limerick City and County Council's Media Communications Plan and prepare an initial draft communication. All media statements are to be approved by the Controller of Operations. If required, establish a Media Briefing Centre in con-junction with Aughinish Alumina Ltd.
4.	Establish on-site contact with the Aughinish Alumina Ltd. Environmental Co-ordinator at the designated Meeting Point.
5.	Confirm the Rendezvous Point (RVP) to be used with the Aughinish Alumina Ltd. Environmental Co-ordinator.
6.	Limerick City & County Council to liaise, **as required**, with*:- a. An Garda Siochana, b. HSE c. Office of Public Works (OPW) d. Shannon Foynes Port Authority e. The Environmental Protection Agency (EPA) f. National Parks and Wildlife Service (NPWS) g. Inland Fisheries Ireland h. LCCC Local Area Staff * (Refer to Section 9 for contact details)
6.	Carry out a site specific risk assessment for the incident with the Environmental Co-ordinator from Aughinish Alumina Ltd. or deputy and determine what resources are required in the first instance to deal with the incident. This may include monitoring of watercourses adjacent to the BRDA to establish the extent of the impact of the incident. (This may require support from SEA-PT/ Civil Defence and LCCC Laboratory).
7.	Review potential contamination pathways and receptors and Aughinish Alumina Ltd. response. Provide additional resources to facilitate the response as required.

	There is no direct public access to the river along the AAL boundary of the BRDA. However, the public paths on the adjacent side of the river should be managed and secured to prevent pedestrian access to the river. Residents local to the Robertstown River should also be advised of the situation as per Section 6 of this plan. This may also include ambulance where there is risk to personnel, fire tender where pumping arrangements may be required and machinery/materials to strengthen and maintain earth barriers to limit contamination pathways. Provide relevant information to responding units as it becomes available.
8.	Establish affected BRDA area.
9.	Establish an Operational Plan.
10.	Consult with the other responding agencies and Aughinish Alumina Ltd. about what action should be taken to communicate the conclusion of the incident and the "all clear" to the public.

2.3 An Garda Síochána (AGS)

	KEY ACTIONS – AN GARDA SÍOCHÁNA
1.	Consider the requirement to declare a Major Emergency as per An Garda Síochána Major Emergency Plan for the division.
	If a Major Emergency is NOT declared. Limerick City & County Council may request key actions from AGS as follows:
2.	Establish the requirement to have a Garda Siochána officer-in-charge at the site.
3.	Establish clear and robust communications with An Garda Síochána officer-in-charge at the site.
4.	Establish communications with other responding agencies. (Include Media Liaison Officer contact with other agencies)
5.	Activate a Traffic Management Plan (where required).
6.	Pass to the Garda Press Office any necessary warning to the public, in accordance with the Limerick City & County Inter-Agency Media Plan and Section 6.0 of this External Emergency Plan.
7.	Depending on information received as to risk scenario, identify safe approach route to the primary Rendezvous Point. Once established, deploy an officer there to liaise with the lead agency Controller of Operations.
8.	Appoint a Garda Controller of Operations who will take command of Garda resources in managing any off site consequences.
9.	Identify locations for Garda Incident Command Vehicle.
10.	Ensure that sufficient Garda resources are deployed to the incident jointly with Aughinish Alumina Ltd. and other responding agencies.
11.	Consider what action should be taken to communicate the conclusion of the incident and the "All Clear" to the public.
12.	Manage personnel when they arrive at the assembly points.

2.4 Health Service Executive (HSE) – West

KEY ACTIONS – HEALTH SERVICE EXECUTIVE -WEST	
1.	Consider the need to declare a Major Emergency as per the Health Service Executive (West) Major Emergency Plan.
	If a Major Emergency is NOT declared. Limerick City & County Council may request key actions from HSE as follows:
2.	Obtain more detailed information regarding the incident from the Operator, or the other Principal Response Agencies, as appropriate.
3.	Provide relevant information to responding units, as it becomes available.
4.	Provide all responding staff with information pertaining to Health & Safety, danger area and need for personal protective equipment.
5.	Respond to designated RVP using pre-determined designated routes.
6.	Alert University Hospital Limerick, UHL Dooradoyle.
7.	Alert National Emergency Operations Centre (NEOC)
8.	Consider the mobilisation of the Decontamination Unit
9.	Determine availability of on-site facilities for:- • Casualty Management • Decontamination

2.5 Health Service Executive – (West) On-Site

KEY ACTIONS – HEALTH SERVICE EXECUTIVE –WEST (ON-SITE)	
The senior HSE Ambulance Officer at the site, if required should:-	
1.	Report to National Emergency Operations Centre (NEOC) using ETHANE.
2.	Act as HSE Controller of Operations, if required.
3.	Meet Controllers of Operations at the predetermined On-site Co-ordination Centre.
4.	In consultation with the Controller of Operators, agree locations for Incident Control, Casualty Clearing Station, Ambulance Loading Point, Body Holding Area and HSE Holding Area, as appropriate.
5.	Prepare a report from the site for the Area Crisis Management Team, using the normal reporting structure, and provide further updates, if appropriate.
6.	Request the activation of additional HSE services through the Ambulance Management Team to the HSE Area Crisis Management Team, if appropriate.
7.	Liaise with other HSE services if required.
8.	Consider the mobilisation of the Decontamination Unit.
9.	Update the National Emergency Operations Centre (NEOC), on a regular basis, with information on the status of the incident, numbers and types of casualties, dispatch of casualties to hospitals, etc.

3.0 ON-SITE INFORMATION

3.1 Details of Materials present at BRDA, Aughinish Alumina Ltd.

This plan has been prepared to respond to major incidents involving materials that are present at BRDA, Aughinish Alumina Ltd. The materials concerned are as follows:

<table>
<tr><th>Substance</th><th>Comments / Data relevant to Relevant Materials</th></tr>
<tr><td>Red Mud</td><td>This is the principal by-product of the alumina extraction process. It is a red mud, a reddish brown bauxite residue which remains after the extraction process and which derives its colour from the iron oxide content. It is characterised by an alkaline pH (~11) due to the presence of residual caustic soda from the alumina extraction process. The mud is classified as a non-hazardous waste (EWC 01 03 09) and its typical analysis is:
<table>
<tr><th>Dry Basis</th><th>Red Mud %</th></tr>
<tr><td>Iron oxide (Fe2O3)</td><td>45</td></tr>
<tr><td>Alumina (Al2O3)</td><td>20</td></tr>
<tr><td>Silicon dioxide (SiO2)</td><td>11</td></tr>
<tr><td>Titanium dioxide (TiO2)</td><td>10</td></tr>
<tr><td>Calcium oxide (CaO)</td><td>7</td></tr>
<tr><td>Sodium oxide (Na2O)</td><td>6</td></tr>
<tr><td>P2O5</td><td>0.4</td></tr>
<tr><td>Cr2O3</td><td>0.3</td></tr>
<tr><td>MgO</td><td>0.1</td></tr>
<tr><td>MnO</td><td>0.05</td></tr>
</table></td></tr>
<tr><td>Alkaline Water</td><td>Run-off from the surface of the BRDA is also alkaline due to its contact with the mud, this collects into the perimeter channel and also has a pH of <11.5. During storms with heavy rainfall, the pH will be reduced and closer to pH 11.</td></tr>
</table>

Table 3.1: Summary of Materials at BRDA

3.3.1 Human Health

Both the red mud slurry and associated run-off water are alkaline in nature (mud with a pH of 10.5-11 and water with a pH of <11.5). Direct contact with either of these substances can result in skin and eye irritation and possible worsening of any pre-existing skin disorders. This may be from direct contact from splashes while working adjacent to the alkaline water channels.

3.3.2 Environmental Impact

Alkaline water release into the Estuary or Robertstown Creek could have an effect on aquatic life. The communities most likely to be impacted would be sessile sublittoral and littoral communities and benthic communities. This would include barnacles, mussels, oysters and shore crabs. Larger mobile species such as dolphins, salmon, otters and shore birds can easily move on to other areas away from the effects of any pollutant.

It is expected that the impact of any alkaline water release would be minimal due to the assimilative capacity of the large watercourse and the tidal influence. Laboratory testing indicates that at a ratio of 1:1 water with pH of <11.5 (such as that contained in perimeter channels) and water with pH of 8.2 (Estuary Water) neutralise to a pH of 10. At a ratio of 25:1 the resulting pH would be 9.
Sampling of the waters would be undertaken to determine any increase in alkalinity and sampling would be continued until such time as the baseline alkalinity is re-established. Landowners adjacent to the potential affected areas (shown in Appendix F) would be notified of any risk.

The release of red mud or alkaline water could also introduce increased suspended solids to the watercourses. This could result in increased siltation and a greater risk of smothering of organisms and habitats.

3.4 Possible Major Accident Scenarios for Aughinish Alumina Ltd.

The major accident scenarios which are considered for this facility are tabulated below and are discussed in more detail in Appendix E of this External Emergency Plan.

It is noted that there is instrumentation present in the perimeter channels and that regular inspections are carried out throughout the day/night of the BRDA by AAL staff. Therefore, it is expected that any breach/failure would be identified soon after occurring. There is also CCTV present in the BRDA

It is also noted that the outfall from the lowlands of the BRDA is via a penstock control, which by design is easy to close, and a tidal flap valve.

Scenario	Description
1.	Release of alkaline waste water in the Perimeter Interceptor Channel and over the top of the Outer Perimeter Embankment Wall of the Phase 1 BRDA.
2.	Release of red mud slurry into the Perimeter Interceptor Channel and over the top of the Outer Perimeter Embankment Wall of the Phase 1 BRDA.

Table 3.4: Summary of Major Accident Scenarios for Aughinish Alumina Ltd.

4.0 INFORMATION FOR RESPONSE AGENCIES

4.1 The Specified Area

The Specified Area is the area which is liable to be affected by a major accident at the establishment. This area has been determined by Golder Associates in preparing the Risk Assessment and Break-out study of the BRDA.

The impact of a discharge via a sluice outlet known as "OPW Sluice" to the Robertstown Creek has also been considered. The impact of this discharge is dependent on the flow rate via the sluice and while it is anticipated that the assimilative capacity of the river will ensure there is minimal risk, which would be confirmed by on-site testing, by way of precaution, those living within a 100m distance from the high water level should be alerted in the event of any such discharge.

The Specified Area for BRDA, Aughinish Alumina Ltd.is outlined in Appendix C of this plan.

Appendix F details those landowners located within the Specified Area or deemed to be sufficiently close to warrant notification in the event of an incident.

4.2 The External Emergency Planning Zone

The Major Accident Scenarios are outlined in Section 3.4 of this plan. The landowners to be notified are detailed in Appendix F. Once the exact extent of the incident is established, the Controller of Operations may decide to amend the zones and to facilitate the movement of traffic and local community.

4.3 Details of Site Access and Egress Routes

4.3.1 Primary Access

The primary access and egress route to the BRDA at Aughinish Alumina Ltd.is from the N69 from the Askeaton side (East) via Local Road L1234 and into the main entrance of Aughinish Alumina Ltd. This is shown in Appendix B of this plan.

4.3.2 Alternative Access

The alternative access and egress route to the Aughinish Alumina Ltd. facility is from the N69 from the Foynes side (West) via Local Road L1234 into the main entrance. This is shown in Appendix B of this plan.

4.4 Location of the Primary Rendezvous Point

The primary Rendezvous Point (RVP) is situated at the carpark adjacent to the Reception/Security building (Area 79). This location is outlined on the site layout plan shown in Appendix B of this plan.

4.5 Location of the On-Site Co-ordination Centre

On declaration of a Major Emergency, the location of the On-site Co-ordination Centre (OSCC) has been identified as:

- **Conference Room: Reception / Security Building (Area 79) at Aughinish Alumina Ltd.**

This is identified in Appendix B of this plan.

4.6 Adjacent Buildings

There are a total of 13 private dwellings within 100m of the Robertstown Creek and these are shown in Appendix F.

4.7 Details of Environmentally Sensitive Areas

The Specified Area associated with the BRDA includes the Lower River Shannon Special Area of Conservation (SAC). In addition the Specified Area includes the River Shannon and Fergus Estuaries Special Protection Area (SPA) and the proposed National Heritage Area (pNHA) of Inner Shannon Estuary – South Shore

Details about these environmentally sensitive areas are described in Appendix E.

4.8 Details of Land Use

The use of land surrounding BRDA - Aughinish Alumina Ltd. is identified as landscaped buffer area with the Limerick City & County Council Shannon Estuary Water Treatment Works to the South East of the BRDA.

4.9 Hazards to People in the Area

There are a number of residential dwellings within a 100m distance from the high water level of Robertstown River. People may be at risk if they come in contact with waters with high pH as per Section 3.3.1 of this External Emergency Plan.

4.10 Specific Hazards to the Environment

See 3.3.2

5.0 INFORMATION AVAILABLE TO THE PUBLIC

5.1 Information provided to the public prior to an incident occurring

Any persons occupying the specified area will be informed by Aughinish Alumina Ltd. in the event of an actual or threatened major emergency.

The defined specified area is entirely in the ownership of Aughinish Alumina Ltd. and therefore the occupants will primarily consist of Aughinish Alumina Ltd. staff and/or any other occupants of the lands.

Separately, Limerick City & County Council has defined an Area which is adjacent to the Specified Area and any residents within this area will be provided with information advising of the procedures to be taken in the event of an actual or threatened major emergency.

The information issued beforehand advises the public to:

- Avoid contact with watercourses in the area.
- Follow any instructions from the Principal Response Agencies (HSE, Gardai, Limerick City & County Council)

5.2 When the Information will be issued

An information leaflet containing all the relevant information has been provided to those residents located with a 100m distance from the high water level of Robertstown River. An updated version of this leaflet will issue as part of the review of External Emergency Plan.

5.3 Method of Providing Information to the public

The relevant information will be provided to the public using the following means:

- An information leaflet, produced by Limerick City & County Council, distributed to households in the area.

6.0 WARNING AND INFORMING THE PUBLIC DURING AN INCIDENT

6.1 How the Public will be notified of an Incident

Following the determination of the extent of the incident, Limerick City & County Council will inform the public of an incident by directly contacting people residing within the 100m high water level. (Appendix F).

6.2 How the Public will be kept Informed during an Incident

Information regarding the emergency will be communicated using media such as house-to-house visits and/or direct telephone.

Procedures will be put in place by the responding agencies to keep the public informed during and after an incident. This is outlined in Section 8.

6.3 How the Public will be notified of the 'ALL CLEAR'

Where a **Major Emergency has been declared**, the decision to stand down the incident at the site, and to announce an "All Clear" to the public, will be taken by the On Site Co-ordinator, in consultation with the other Controllers of Operations at the site and the Local Co-ordination Group.

Where a **Major Emergency has NOT been declared**, the decision to stand down this External Emergency Plan and to announce an "All Clear" to the public will be taken by Limerick City & County Council, in consultation with the Environmental Co-ordinator of Aughinish Alumina Ltd.

The methods chosen to notify the 'All Clear' for Aughinish Alumina Ltd. will depend on the nature and extent of the incident and it`s impact on the public.

Notwithstanding that the site has been declared clear, the Controller of Operations together with the a Media Liaison Officer(s) should prepare and issue advice on any measures necessary for members of the public to manage the aftermath of the incident.

7.0 WORKING WITH THE MEDIA

7.1 Inter-Agency Media Plan

Limerick City and County Council shall activate its Media Communications Plan on activation of the External Emergency Plan.

In the event of a major emergency, the Mid-West Inter-Agency Media Communications Plan shall be activated and the Media Liaison Officers from the Principal Response Agencies shall initiate a teleconference to decide on the appropriate response.

The activities of the Media Liaison Officers at the site will be co-ordinated by the Media Liaison Officer of Limerick City & County Council. All statements to the media should be approved by the On-Site Co-ordinator.

If required, Limerick City & County Council, in conjunction with Aughinish Alumina Ltd., shall establish a Media Briefing Centre.

7.2 Co-ordination with Aughinish Alumina Ltd. Media Strategy

The media liaison contact provided by Aughinish Alumina Ltd. should liaise with the Media Liaison Officers of Limerick City & County Council to ensure a co-ordinated response to the incident.

8.0 RECOVERY

8.1 Clean-up Operations

RUSAL Aughinish BRDA Containment Failure Emergency Procedure details suitable and sufficient provisions for the restoration and clean up of the environment within the site ownership following a major accident.

Environmental Clean-Up operations required where there is a discharge to the Estuary and/or Robertstown River will be determined following testing of the waters to confirm contamination.

8.2 Organisations to be consulted

Contact Details		
Name	**Address**	**Contact Number**
Environmental Protection Agency (EPA)	P.O. Box 3000, Johnstown Castle Estate, Wexford	Ph: 053-9160600 Fax: 053-9160699 Emergency Pager Number: 0890 335599
HSE (Public Health)	Department of Public Health, HSE, Mount Kennett House, Henry Street, Limerick	061 - 483338
National Parks & Wildlife Service (NPWS)	7 Ely Place, Dublin 2.	01-8883242

8.3 Arrangements that the Site Operator has to support the Community following an Incident

To support the Community following the incident, Aughinish Alumina Ltd. will ensure that they have all relevant insurances in place.

8.4 Arrangements that An Garda Síochána will put in place to support the Community following an Incident

An Garda Síochána shall provide all necessary and appropriate information on the investigations, as soon as it is possible.

Otherwise, An Gárda Síochána will comply with the provisions of the Major Emergency Plan, as applicable in the circumstances during the recovery phase.

8.5 Arrangements that Health Service Executive will put in place to support the Community following an Incident

The HSE shall assess the health needs of the community and consider the scale of immediate and ongoing needs for assistance in the circumstances of the emergency. The following needs in particular will be considered:

- The health needs of any persons affected by the emergency.
- Provide a point of contact for the provision of information and for dealing with the health concerns of the community.
- Provide advice on environmental health in the circumstances of the emergency

8.6 Arrangements that Limerick City & County Council will put in place to support the Community following an Incident

Limerick City & County Council shall:

- Make arrangements to provide appropriate support, assistance and advice to people affected by the emergency.
- Establish a list, in priority order, of remedial works / actions, with a view to dealing with such works / actions in a speedy and efficient manner.
- Establish any remedial works / actions, which are outside its own control / function, and shall determine the speediest means of their alleviation, including legal remedy, if necessary.
- Advise on testing requirements, carrying out the clean-up and restoration in the event of a major environmental emergency.
- Prepare a post-incident evaluation and a resulting Incident Report for circulation to all other agencies.

9.0 CONTACT DIRECTORY

NOTE: A more comprehensive contact list is provided in each of the Principal Response Agencies Major Emergency Plan.

Aughinish Alumina Ltd.		
Name	**Position**	**Contact Number**
Aughinish Alumina Ltd.		Phone: 061 604000 Fax: 061 604090
Louise Clune	Environmental Manager	Mobile: 0861064941
Michael O' Toole	Human Resources, Health, Safety and Community Affairs Manager	Mobile: 087-8604567
Please refer to Section 8 of RUSAL Aughinish BRDA Containment Failure Emergency Procedure for more contact details.		

Principal Response Agencies		
Limerick City & County Council	County Hall, Dooradoyle	Office Hours: 061-556000 Out of Office Hours: 061-417833
An Garda Síochána	Henry Street Garda Station	061-212400
Health Service Executive	Emergency Management Office, Merlin Park Hospital, Galway.	091-775080

Media Communication Team		
Denis Tierney	Communications Officer, Limerick City & County Council	061-557224 / 087-0907037
Michael O'Toole	Human Resources, Health, Safety and Community Affairs Manager, Aughinish Alumina Ltd.	061-604000 / 087-8604567
Office of Communications & Corporate Services	EPA	053-9170770

National Parks & Wildlife Service	
Eamonn Meskill – Regional Manager	064 6631440

Environmental Protection Agency (EPA)	
EPA -Wexford	053-9160600

EPA - Cork – OEE Inspector	021 4875540
Emergency Pager Number	1890 355 599

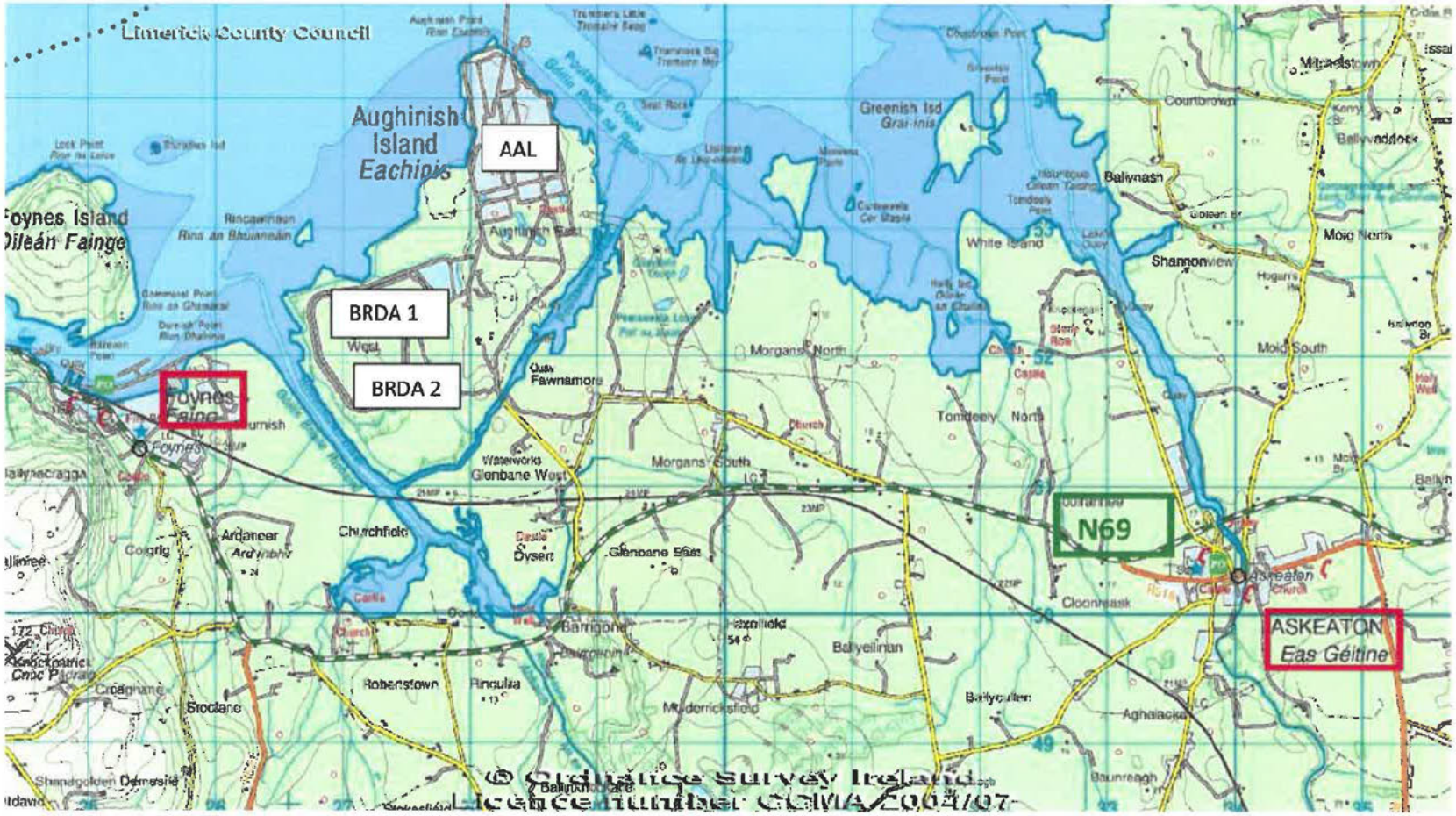
Health Service Executive	
Ambulance Service	999/112
University Hospital Limerick UHL Dooradoyle, Co. Limerick	Ph: 061-301111 Fax: 061-301165
Regional Emergency Management Office	091-775080

Medical Assistance	
Croagh Medical Centre	069-63444
Dr. Susanne Fitzgibbon – Askeaton	061-392267
Foynes Clinic	069-65196
Shannon Doc	1850 212999

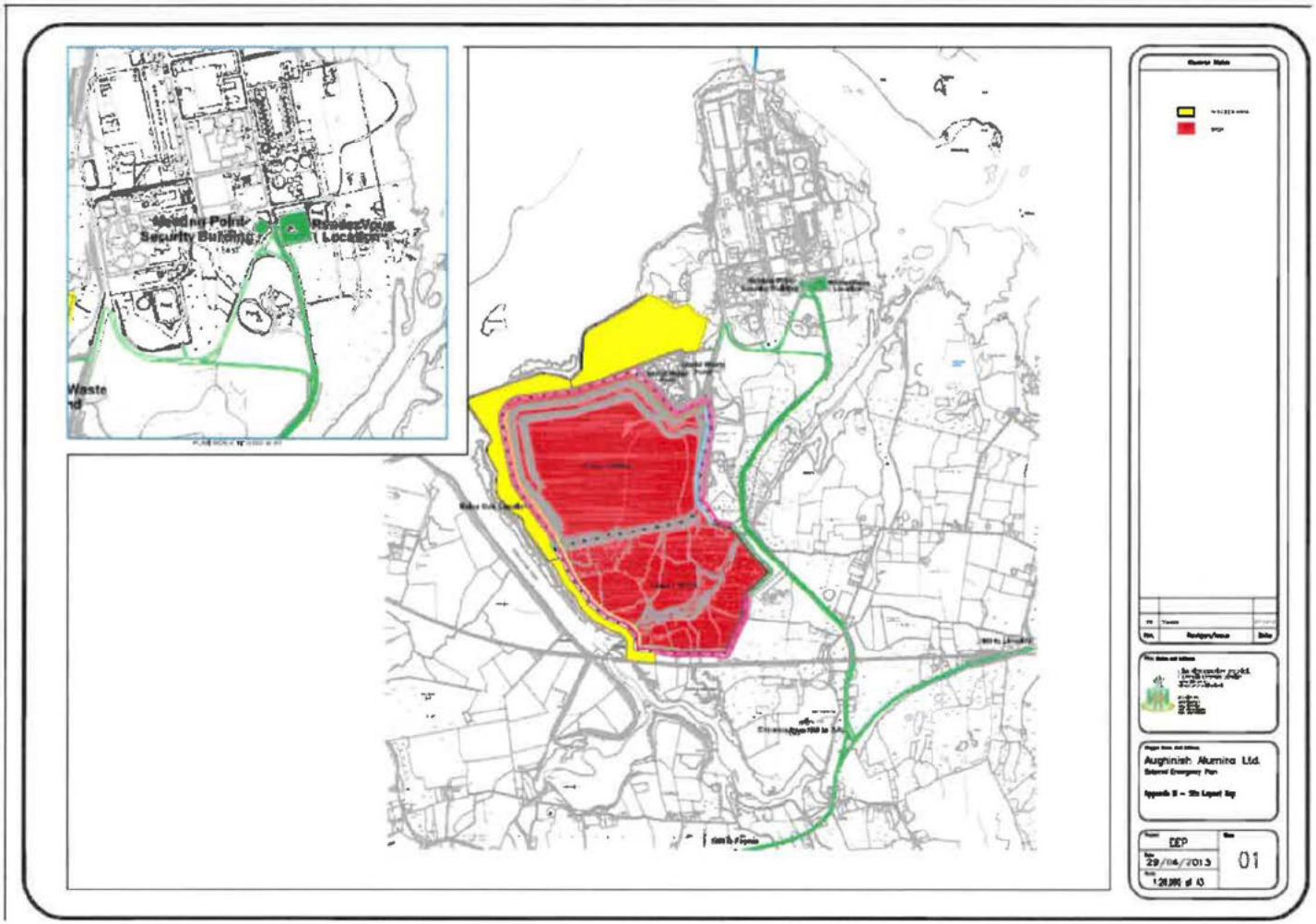
10.0 SCHEDULE OF APPENDICES

Appendix	Title
A	Site Location Map
B	Site Layout Map
C	Specified Area
D	Environmentally Sensitive Areas
E	Summary of Risk Assessment and Break-Out Study by AAL
F	Residential Properties to be Informed Prior to and during an Incident
G	Definitions

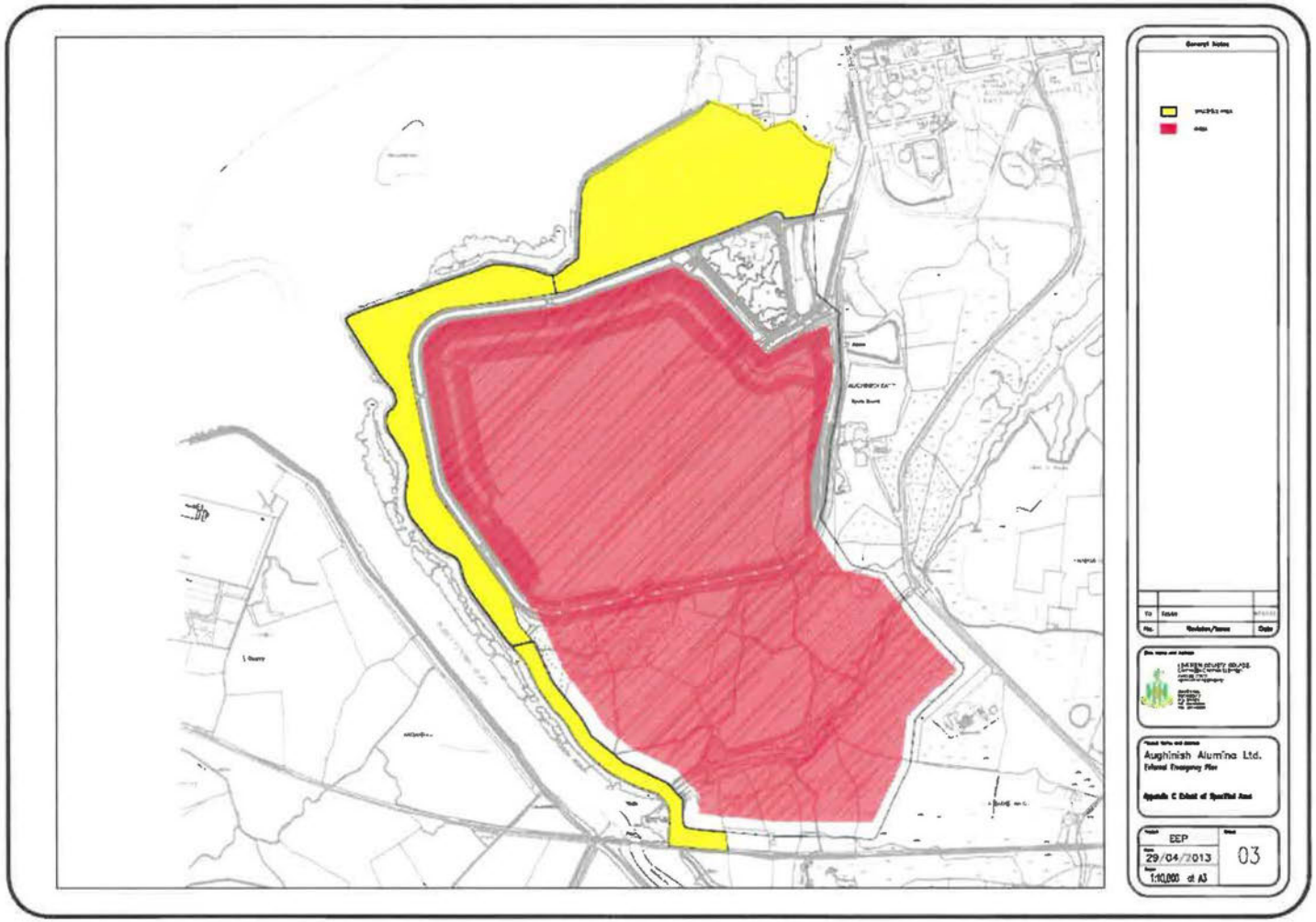
APPENDIX A -SITE LOCATION MAP



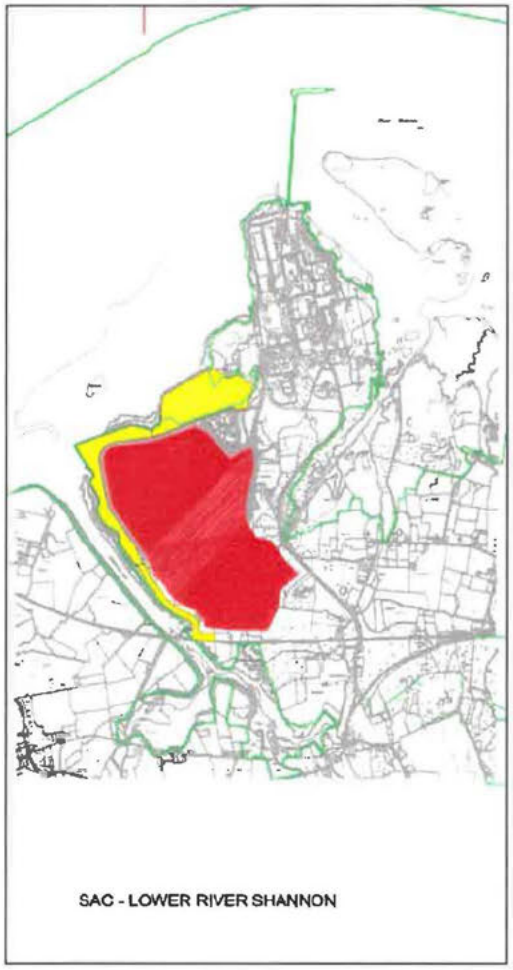
APPENDIX B -SITE LAYOUT MAP



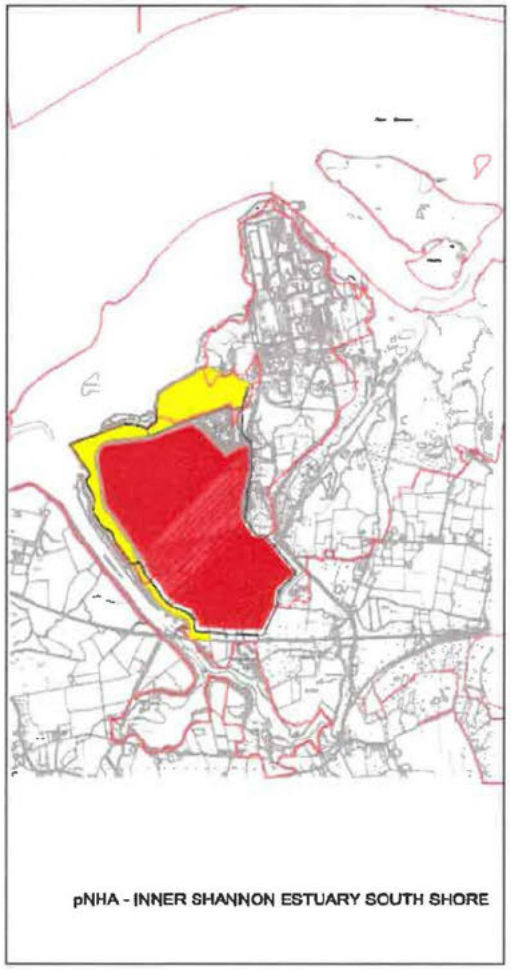
APPENDIX C –SPECIFIED AREA



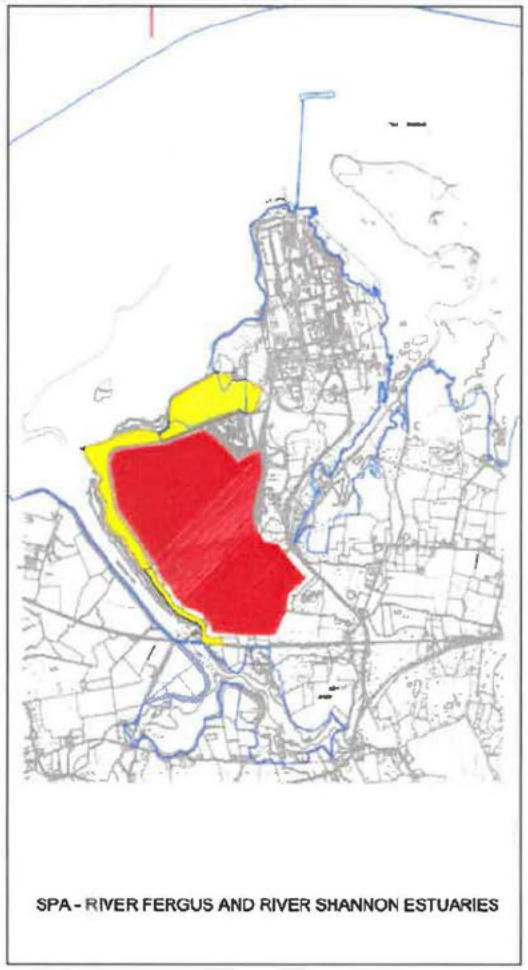
APPENDIX D – ENVIRONMENTALLY SENSITIVE AREAS



SAC - LOWER RIVER SHANNON



pNHA - INNER SHANNON ESTUARY SOUTH SHORE



SPA - RIVER FERGUS AND RIVER SHANNON ESTUARIES

APPENDIX E – SUMMARY OF RISK ASSESSMENT AND BREAK OUT STUDY

Note: The following summary has been prepared by Limerick City and County Council from information provided in the Executive Summary of the Golder Associates (UK)Risk Assessment and Break-Out Study, prepared in March 2013 for Aughinish Alumina Ltd..

The risk assessment and break-out study prepared on behalf of Aughinish Alumina Ltd (AAL) and submitted to the EPA was scoped to provide an indication of the possible mechanisms of catastrophic failure of the dam wall that could lead to a breach of the Bauxite Residue Disposal Area (BRDA), Storm Water Pond (SWP), Liquid Waste Pond (LWP) and the Perimeter Interceptor Channel (PIC), resulting in the subsequent release of waste water and/or liquefied red mud slurry to the downstream environment.

The Risk Assessment considered an estimation of the probability of failure occurring, an indication of the route and geometry of a flow of water and liquefied red mud slurry following a breach of the dam wall of the BRDA or ancillary structures and details of procedures to mitigate the risk of the failure scenarios identified.

The key components of the AAL BRDA are:

- Low Permeability Outer Perimeter Embankment Wall;
- Permeable Inner Perimeter Embankment Wall;
- Perimeter Interceptor Channel;
- Composite Lined System throughout the Phase 1 Extension and Phase 2 BRDA;
- Stage Raises;
- Upper level bench to reduce the overall side slopes
- Protection from the Robertstown River and River Shannon by a flood tidal defence berm

The risk assessment considered the potential "pathways" of the BRDA dam wall breaks that could conceivably result in release of significant volumes of material to the downstream environment.

The main failure modes or events identified leading to the loss of red mud and/or water into the environment:

- Loss of containment, through slope or foundation failure, or erosion;
- Overtopping of the SWP, LWP and PIC; and
- Failure through storm surge.

Having established a number of cause/consequence trees that model the potential pathways from the hazards to the target, probabilities were assigned to the cause/consequence trees. The probabilities were assigned on the basis of professional judgement and calculations, where appropriate.

A general guide used to describe annual probability of occurrences used is given below.

Description of Probabilities

Annual Probability of Occurrence	Description
1e-6 (1 in 1 million)	Almost impossible or negligible (no published information on a similar case exists)
1e-5 (1 in 100,000)	Highly improbable (published information exists, but in a slightly different context)
1e-4 (1 in 10,000)	Very Unlikely (it has happened elsewhere, but some time ago)
1e-3 (1 in 1,000)	Unlikely (recorded recently elsewhere)
1e-2 (1 in 100)	Possible (could have occurred already without intervention)
0.1 (1 in 10)	Highly probable (a previous incident of a similar nature has occurred already)
0.2 – 0.5 (1 in 5 to 1 in 2)	Uncertain (nearly equal chance of occurring to that of not occurring)
0.5 - 0.9 (>1 in 2)	Nearly certain (one or more incidents of a similar nature have occurred recently)
1 (or 0.999)	Certain (or as near to, as makes no significant difference)

As a comparison, the average risk of death from various human causes and natural accidents is tabulated below for data from the USA.

Description of Probabilities

Annual Probability of Occurrence	Description of Accident Resulting in Death
1E-7 (1 in 10 million)	Falling Aircraft
5E-7 (1 in 2 million)	Lightning Strike
6.25E-6 (1 in 160,000)	Electrocution
1E-5 (1 in 100,000)	Air Travel
3.3E-5 (1 in 30,000)	Drowning
4E-5 (1 in 25,000)	Fire and Hot Substances
5E-5 (1 in 20,000)	Struck By A Motor Vehicle
1E-4 (1 in 10,000)	Falls
2.0E-4 (1 in 5,000)	Influenza
2.5E-4 (1 in 4,000)	Motor Vehicle

Probability of failure and stability factors of safety have been investigated for various soil slopes in dams, embankments, cuts and excavations designed with usual factors of safety and site investigation procedures.

Based on this work the annual probability of failure for given factors of safety can be related and are tabulated below.

Probability of Failure and Factor of Safety

Annual Probability of Failure	Factor of Safety
1E-6 (1 in 1 million)	2.0
1E-5 (1 in 100,000)	1.8
1E-4 (1 in 10,000)	1.6
1E-3 (1 in 1,000)	1.4
1E-2 (1 in 100)	1.2
0.1 (1 in 10)	1.0

It was established that the risks associated with containment and wave surge failure for the BRDA are significantly lower in relation to the annual probability of failure for modern engineered embankment dams which is about **1.65E-4**[3]

The probabilities for release of red mud from the BRDA were deemed to be negligible. These low probabilities reflect the absence of water on the BRDA and the shallow slopes resulting in relatively safe stable conditions.

For the Storm Water Pond, the annual risk from overtopping and wave surge failure was shown to be less than that for a modern engineered dam at **1.65E-4**. However, the probability of containment failure is slightly higher but has an equivalent stability factor of safety of **1.44** which is satisfactory.
The overall probability of release of alkaline water from the Storm Water Pond is slightly higher than that for a modern engineered dam and equates to a stability factor of safety of **1.41** which is satisfactory.

The Liquid Waste Pond has a similar but slightly lower overall annual probability risk which equates to a stability factor of safety of **1.49** which is satisfactory

In the negligible likelihood of a BRDA failure, the theoretical volume of red mud that could be released from the BRDA is estimated to be in the order of 15,000 m3 to 30,000 m3. The flow model used indicated that the red mud could move a distance of 5m for the farmed red mud and 80 metres for red mud which has liquefied. The flood tidal defence berm will be able to retain the liquefiable red mud provided it has not been washed away as a result of tidal surge. The volume of water released from the SWP, LWP and PIC will depend on their inventory at the time of failure although it is likely to be at their maximum level. The worst case for the SWP and LWP would relate to the facilities being completely full with nearly 300,000m3 of water. If released, the water would be retained within the FTDB although there could be escape through the sluice gate valve into the Robertstown River. Similarly, for the two number PICs, when

[3] *The annual probability of failure for modern engineered embankment dams is **1.65E-4**which equates to a factor of safety in terms of stability of approximately **1.56** based on the data above. The source of dam failure data used in the study is from ICOLD's (International Committee on Large Dams) Bulletin 99 and from the Wise Uranium Project which collate data on dam failures for water retaining dams, tailings dam incidents. In addition, ICOLD's Bulletin 121 assesses the risk of dangerous occurrences associated with tailings dams.*

full retains a combined volume of approximately 226,000m3 of water. If released, the water would be retained within the FTDB although again there could be escape through the sluice gate valve into the Robertstown River.

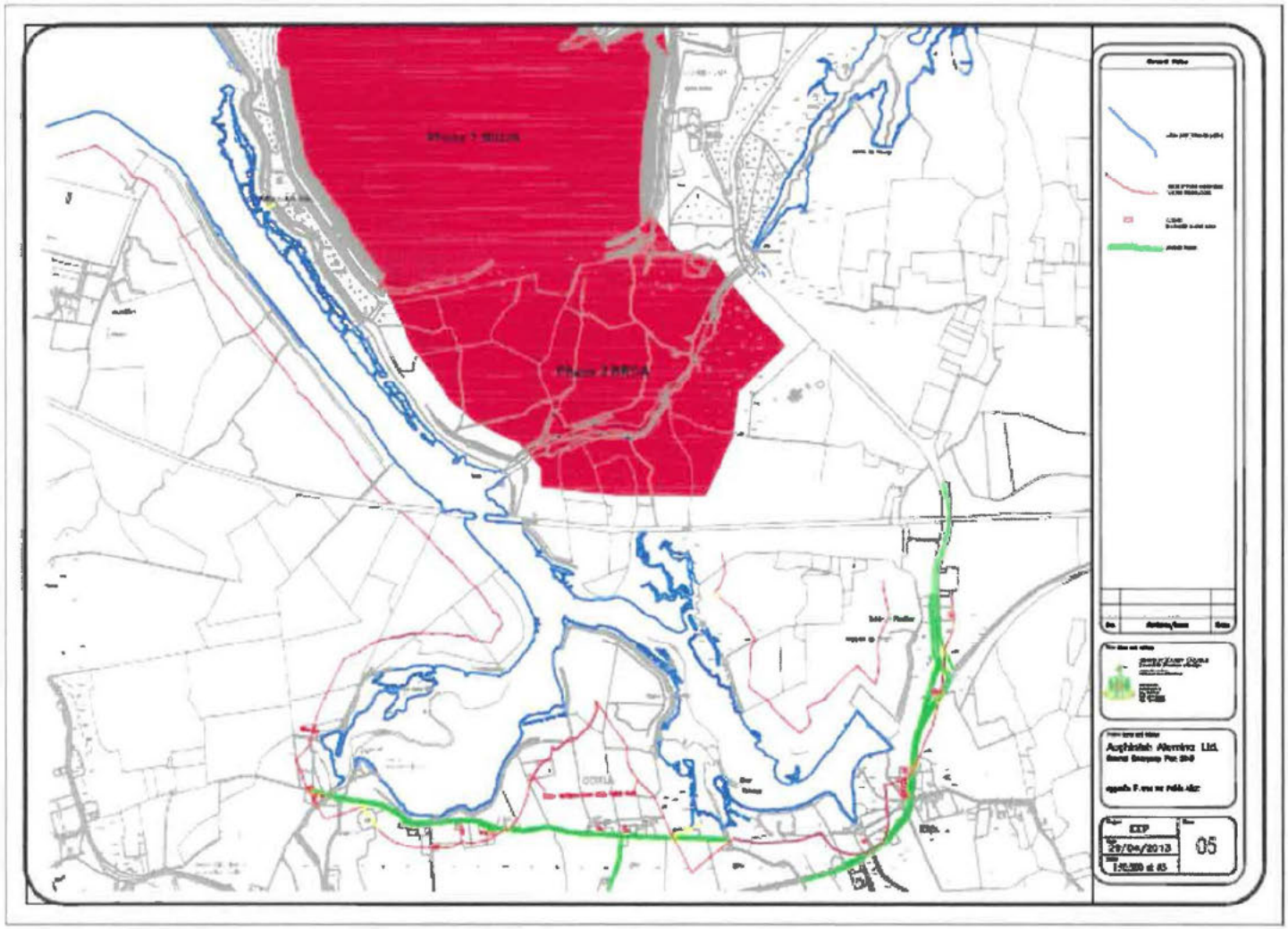
The most important hazards identified in the study by the risk analysis relate to:

- Displacement of alkaline water in the PIC as a result of wave surge without breaching the embankment wall and indirectly displacement of the alkaline water in the SWP and waste water in the LWP.

- Slope failure of the containment walls for the SWP, LWP, and the Outer Perimeter Wall under static load conditions; and

- Containment failure from the 2200 year wave surge in the PIC.

APPENDIX F - Residential Properties to be Informed Prior to and during an Incident



APPENDIX G – DEFINITIONS

Definitions are taken from A Framework for Major Emergency Management – Guidance Document 10: *A Guide for PRA Local Competent Authorities under S.I No.209 of 2015 European Communities (Control of Major Accident Hazards Involving Dangerous Substances) Regulations 2015- October 2015,* except where amended as shown*

Controller of Operations	The person given authority by a principal response agency to control all elements of its activities at and about the site.
Crisis Management Team	A tactical level management group, which consists of senior managers from within the principal response agency, which is assembled to manage a crisis and deal with issues arising for the agency both during the emergency and the subsequent recovery phase.
Danger Area	Areas where there is a definite risk to rescue personnel, over and above that which would normally pertain at emergency operations.
Decontamination	A procedure employed to remove hazardous materials from people and equipment.
Holding Area	An area at the site, to which resources and personnel, which are not immediately required, are directed to await deployment.
Information Management System	The Information Management System is to assemble available data and to present decision makers with relevant information as a sound basis for their decision making function. The Information Management System is structured into four fields, which consist

	of Recognised Current Situation, Key Issues, Strategic Aim/Priorities and Actions.
Lead Agency	The Principal Response Agency that is assigned the responsibility and mandate for the coordination function in response to a major emergency.
Local Co-ordination Centre	A pre-nominated building, typically at county or subcounty level, with support arrangements in place, and used for meetings of the Local Co-ordination Group.
Local Co-ordination Group	A group of senior representatives from the three Principal Response Agencies (An Garda Síochána, HSE and Local Authority) whose function is to facilitate strategic level co-ordination, make policy decisions, liaise with regional/national level coordination centres, if appropriate, and facilitate the distribution of information to the media and the public.
Major Emergency Plan	A plan prepared by each of the Principal Response Agencies in responding to a major emergency.
Major Emergency	Any event which, usually with little or no warning, causes or threatens death or injury, serious disruption of essential services, or damage to property, the environment or infrastructure beyond the normal capabilities of the principal emergency services in the area in which the event occurs, and requiring the activation of specific additional procedures to ensure effective, co-ordinated response.
Major Accident*	A major accident is an occurrence on site in the course of an operation involving

	the management of extractive waste in any establishment covered by Directive 2006/21/EC 1 , leading to a serious danger to human health and/or the environment, whether immediately or over time, on-site or off-site;
Meeting Point	An agreed location for the initial meeting of the Principal Response Agencies with the site operator.
On-Site Coordinator	The person from the lead agency with the role of coordinating the activities of all agencies responding to an emergency.
On-Site Coordination Centre	Specific area/facility at the Site Control Point where the On-Site Co-ordinator is located and the On-Site Coordination Group meet.
Principal Emergency Services (PES)	The services which respond to normal emergencies in Ireland, namely An Garda Síochána, the Ambulance Service and the Fire Service.
Principal Response Agencies (PRA)	The agencies designated by the Government to respond to Major Emergencies i.e. An Garda Síochána, the Health Service Executive and the Local Authorities.
Rendezvous Point (RVP)	The Rendezvous Point is the location to which all resources responding to the emergency site are directed in the first instance. An Garda Síochána will organise the Rendezvous Point. Other services may have one of their officers present to direct responding vehicles into action or to that service's Holding Area.

Appendix 7.3: Human Health Assessment

AUGHINISH ALUMINA LTD.

HUMAN HEALTH ASSESSMENT FOR BAUXITE RESIDUE AND SALT CAKE

NOVEMBER 26, 2021

ISSUE TO CLIENT

HUMAN HEALTH ASSESSMENT FOR BAUXITE RESIDUE AND SALT CAKE

AUGHINISH ALUMINA LTD.

PROJECT NO.: 211-09062-02
DATE: NOVEMBER 26, 2021

WSP
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T: +1 519 743-8778
WSP.COM

November 26, 2021

ISSUE TO CLIENT

AUGHINISH ALUMINA LTD.

Attention:

Dear Sir / Madam:

Subject: **Human Health Assessment for Bauxite Residue and Salt Cake in Support of the Environmental Impact Assessment for the Expansion of the Alumina Production Facility, Askeaton, County of Limerick, Ireland**

WSP Canada Inc. (WSP), in collaboration with Golder Associates Ltd. (a member of WSP Canada Inc.), has been retained to prepare a Human Health Assessment (HHA) for the bauxite residue and salt cake produced as a by-product from the existing alumina production facility located in the townlands of Aughinish East, Aughinish West, Island Mac Teige, Glenbane West, and Fawnamore at or adjacent to Aughinish Island, Askeaton, County of Limerick (herein referred to as "the Project"). The Project is owned and operated by Aughinish Alumina Ltd ("AAL"). The HHA has been completed in support of the Environmental Impact Assessment (EIA) that forms part of the Planning Application by AAL.

Please find attached for your review and comment, the draft HHA, including tables, figures, and appendices.

Sincerely,

Theresa Repaso-Subang, BSc, DABT, ERT, QPRA
Senior Technical Lead, Toxicology & Risk Assessment

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Project Manager
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The report is intended to be used in its entirety. No excerpts may be taken to be representative of the findings in the assessment.

The conclusions presented in this report are based on work performed by trained, professional and technical staff, in accordance with their reasonable interpretation of current and accepted engineering and scientific practices at the time the work was performed.

The content and opinions contained in the present report are based on the observations and/or information available to WSP at the time of preparation, using investigation techniques and engineering analysis methods consistent with those ordinarily exercised by WSP and other engineering/scientific practitioners working under similar conditions, and subject to the same time, financial and physical constraints applicable to this project.

The intended recipient is solely responsible for the disclosure of any information contained in this report. If a third party makes use of, relies on, or makes decisions in accordance with this report, said third party is solely responsible for such use, reliance or decisions. WSP does not accept responsibility for damages, if any, suffered by any third party as a result of decisions made or actions taken by said third party based on this report.

In preparing this report, WSP has relied in good faith on information provided by others, as noted in the report. WSP has reasonably assumed that the information provided is correct and WSP is not responsible for the accuracy or completeness of such information.

This limitations statement is considered an integral part of this report.

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LIST OF ACRONYMS

ACRONYM	DEFINITION
AAL	Aughinish Alumina Limited
AAQC	Ambient Air Quality Criteria
AAQO	Ambient Air Quality Objective
ACGIH	American Conference of Government Industrial Hygienists
ACS	American Cancer Society
AENV	Alberta Environment
AMCV	Air Monitoring Comparison Value
AML	Acute Myeloid Leukemia
ANL	Acute Nonlymphocytic Leukemia
AQA	Air Quality Assessment
AQO	Air Quality Objective
ATSDR	Agency for Toxic Substances and Disease Registry
AWN	AWN Consulting
BC MoECCS	British Columbia Ministry of Environment and Climate Change Strategy
BRDA	Bauxite Residue Disposal Area
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
Bq	Bequerel
CAAQS	California Ambient Air Quality Standards
Cal OEHHA	California Office of Environmental Health Hazard Assessment
CCME	Canadian Council of Ministers of the Environment
CDC	Centers of Disease Control
COPC	Chemicals of Potential Concern
CSM	Conceptual Site Exposure Model
DABT	Diplomate of the American Board of Toxicology
EC	European Commission
ECHA	European Chemical Agency
EDI	Estimated Daily Intake
EE	Exposure Estimate
EIAR	Environmental Impact Assessment Report

ACRONYM	DEFINITION
EPC	Exposure Point Concentration
ER	Exposure Ratio
ERT	European Registered Toxicologist
ERV	Emergency Room Visits
ESA	Environmental Site Assessment
ESL	Effect Screening Level
ET	Exposure Time
GHS	United Nations Globally Harmonised System of Classification and Labelling of Chemicals
GRAS	Generally Recognized as safe
HA	Hospital Admissions
HHA	Human Health Risk Assessment
HQ	Hazard Quotient
Hr	hour
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICE	Isolated Chicken Eye
ILCR	Incremental Lifetime Cancer Risk
IQ	Intelligence quotient
IUR	Inhalation Unit Risk
kg	Kilogram
mg	milligram
M	meter
mOD	Metres above Ordnance Datum
MV	Metro Vancouver
mSv	microSieverts
NAAQS	National Ambient Air Quality Standard
NO_2	Nitrogen Dioxide
NOAEL	No Observed Adverse Effect Level
NORM	Naturally Occurring Radioactive Material
NRC	National Research Council
OECD	Organisation for Economic Cooperation and Development
ON MECP	Ontario Ministry of Environment, Conservation and Parks
PEC	Predicted Exposure Concentration

ACRONYM	DEFINITION
PM	Particulate Matter
PM_{10}	Coarse Particulate Matter
$PM_{2.5}$	Fine Particulate Matter
PNOS	Particulate (insoluble) Not Otherwise Specified
QPRA	Qualified Person for Risk Assessments
RA	Risk Assessment
REACH	Evaluation, Authorisation and Restriction of Chemicals
POD	Point of Departure
SCDC	Salt Cake Disposal Cell
SF	Slope Factor
TCEQ	Texas Commission on Environmental Quality
TRV	Toxicity Reference Value
µg/m3	Microgram per cubic meter
UF	Uncertainty Factor
URF	Unit risk factor
US EPA	United States Environmental Protection Agency
US FDA	US Food and Drug Administration
VOC	Volatile Organic Compound
WHO	World Health Organization

EXECUTIVE SUMMARY

Aughinish Alumina Limited (AAL) retained WSP Canada Inc. (WSP), in collaboration with Golder Associates Ireland Ltd. (Golder), to complete this Human Health Assessment (HHA) to support the Environmental Impact Assessment for the proposed expansion of the Bauxite Residue Disposal Area (BRDA) and the Salt Cake Disposal Cell (SCDC). AAL operates a long-established alumina plant, located on Aughinish Island on the southern side of the Shannon Estuary near the village of Foynes, County of Limerick. The landholding extends to c. 601 hectares and is located c. 6 km north-west of Askeaton and c. 30 km west of Limerick City Centre.

Bauxite residue, a by-product of the alumina production process, is deposited within the BRDA located to the south-west of the plant. The BRDA covers an area of approximately 184 hectares (ha). The SCDC, located within the BRDA, is an engineered cell that stores the salt cake hazardous waste created from removing the organic impurities when the bauxite is dissolved. The Project site plan is shown on **Figure 1.1.**

The proposed development consists of works to the BRDA comprising of an expansion to increase its disposal capacity to accommodate additional bauxite residue arising from the continued operation of the permitted alumina plant located on the wider AAL facility. The proposed increase in disposal capacity to the BRDA will result in a proposed increase in height of c.12m above the currently permitted stage 10 level (c. 32m OD) to a final stage 16 level (c. 44m OD). No increase to the existing footprint of the BRDA is proposed.

The proposed method of raising the BRDA will be the upstream method, consistent with the construction methodology for the current BRDA and involves the construction of rock fill embankments (Stages), offset internally, and founded on the previously deposited and farmed bauxite residue, in 2 m high vertical lifts. The overall stack is raised systematically as the stages are filled with bauxite residue, farmed, carbonated, and compacted, prior to deposition of the next layer.

To complete the HHA, WSP evaluated the toxicity of bauxite residue and salt cake by-products, assessed the source-pathway-receptor linkage to understand causal relationship between predicted exposures and bauxite residues, as well as characterized health risks, if any, of nearby human populations with potential exposures released from the Project.

Given that bauxite residues and salt cake waste by-products are mixtures and due to their limited (or absent) toxicology data, a literature search and review was completed for their constituents to determine the toxicology and associated health effects from exposures to solid waste mixtures as well as identify which chemicals of potential concern (or COPCs) will be carried forward for further evaluation in the HHA. All constituents were identified as COPCs for further assessment in the HHA, with exception of those constituents that were listed as "Generally Recognized as Safe" ("GRAS") by the US Food and Drug Administration (FDA).

Those substances listed as GRAS have been concluded to have "***no evidence in the available information …that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future***" (US FDA, 2018).

It was determined that constituents of bauxite residue and salt cake that would be screened out from further assessment included: moisture, Bayer sodalite, Gibbsite, Quartz, Sodium carbonate (baking soda), Carbonate apatite, Sodium bicarbonate (baking soda), Sodium aluminate, Sodium hydroxide, Magnesium oxide, and potassium carbonate. The constituents of bauxite residue and salt cake that were screened out from further evaluation in the HHA totaled 33.5% and 61.5% of the total weight percentage, respectively. **Table 4.1** and **Table 4.2** summarize the compositions of bauxite residue and salt cake, as well as indicate which constituents were carried forward as COPCs.

Before assessing the potential health effects of Project-related emissions, the HHA characterized existing community health (i.e., Limerick County) by referring to several credible health-related sources including a 2015 Health Profile for the City of Limerick, a 2019 Health in Ireland report, and key health statistics from Ireland Central Statistics Office. Collectively, these sources suggested that the death rate for many diseases in Limerick is lower or equivalent to other counties and the national average. Death rates were only marginally higher for diseases such as myocardial infraction and other diseases of the circulatory system, and two times higher for diseases of the blood, blood forming organs, and immunological disorders. However, it is important to note that data between 2009 to 2017 indicates that death rates for these diseases (and many others) are on a steady decline in Limerick.

The human receptors evaluated in the HHA were identified based on land use(s) within the Project Study Area and included sensitive subpopulations such as children and residents. The following human receptors were considered and evaluated in the HHA:

- Young children and teen students in a primary school (Scoil Naisiunta Sheanain);
- Adult workers (e.g., teachers) at the primary school; and,
- Individuals who live in residential communities near the Project.

A toxicological and jurisdictional review of available ambient air exposure limits was completed for all identified COPCs. Health-based TRVs were selected for each COPC and averaging period, if available, based on information obtained during this review.

For non-cancer health endpoints, the findings of the risk analysis concluded the following:

- There are no health concerns associated with exposures to Project-related COPCs for students and teachers at the nearby primary school.
- Predicted health risks for students and teachers at the nearby primary school are associated with exposures to background ambient concentrations of PM_{10} and $PM_{2.5}$; constituting over 45% to as high as 99% of the predicted health risks.
- There are no health concerns associated with exposures to Project-related COPCs for nearby residents, for all life stages (i.e., infancy, toddler, child, teen, and adult).

For cancer health endpoints, the findings of the risk analysis concluded the following:

- Potential inhalation exposures of chromium trioxide, arsenic trioxide and PM_{10} from Project-related emissions are associated with *de minimis* incremental risk of cancer for students and teachers at the primary school as well as nearby residents.

The HHA was carried out to err on the side of caution to ensure that the results are protective of human health. As such, it is important to highlight that the conclusions were based on the following conservative approach that have been applied in the HHA:

- The risk analysis applied worst-case Project emissions of PM_{10} and $PM_{2.5}$ at the Project boundary. That is, all human receptors evaluated in the HHA were assumed to be exposed to maximum 24-hr concentrations, calculated as 90^{th} percentile concentrations, at the Project boundary. In addition, the exposure assessment only considered predicted air concentrations from scenario 1, which represents the earliest stage of BRDA elevation construction and the worst-case predicted air concentrations. Predicted air concentrations show a slight decrease as the BRDA is raised (i.e., with each successive scenario), with the final scenario (5) having the lowest predicted air concentrations as the surface area of the BRDA is significantly reduced compared to the other scenarios. Therefore, using predicted air concentrations from scenario 1 in addition to assuming that human receptors are present at the Project boundary exposed to maximum concentrations for the purpose of the exposure assessment is considered an overly conservative approach, and is likely to overestimate risk.
- These worst-case concentrations were selected to develop the COPC-specific exposure concentrations used for the purpose of the exposure assessment. Given that these concentrations are based along the AAL facility boundary, and that the nearest off-site receptor is located approximately 1.9 kilometres to the west of the AAL facility, use of these worst-case concentrations is considered a conservative approach, and is likely to overestimate risk.
- The HHA assumed that emissions of the bauxite residue and salt cake predominantly occurs as particulates or fugitive dusts. To assess potential exposures to bauxite residue and salt cake, this HHA assumed their constituents will be present in the dusts emitted from the Project at the same percentage composition. That is, the predicted concentration for each COPC is based on the percentage of each COPC modelled PM_{10} (annual and 24-hr) and $PM_{2.5}$ (annual and 24-hr) concentrations to reflect the percentage of each COPC in the dust. Therefore, this HHA assumes that both bauxite residue and salt cake are both present as dust, with levels of their constituents present at the same percentage composition as in the solid waste by-product. This

assumption maintains an overly conservative approach given that the moisture content of both bauxite residue (21%) and salt cake (41% to 46%, with a mean of 44%) are high. The presence of salt cake constituents as particulates or dust is highly unlikely given that moisture content is approximately 50%.

- Conservative assumptions were applied when calculating the exposure estimates (i.e., conservative assumptions for exposure durations and frequencies). For example, residents were assumed to be exposed to predicted exposure concentrations at the Project boundary continuously, for 24-hours, daily.
- Based on the findings of this HHA based on the use of maximum predicted exposure concentrations of PM_{10} and $PM_{2.5}$, and in combination with the use of overly conservative exposure assumptions applied in the risk analysis, bauxite residue and salt cake do not pose a health concern to human receptors in the nearby primary school and nearby residences.

1 INTRODUCTION

1.1 BACKGROUND

Aughinish Alumina Limited (referred to herein as "the Applicant" or "AAL") operates a long-established alumina plant, located on Aughinish Island on the southern side of the Shannon Estuary near the village of Foynes, County of Limerick. The landholding extends to c. 601 hectares and is located c. 6 km north-west of Askeaton and c. 30 km west of Limerick City Centre.

Bauxite residue, a by-product of the alumina production process, is deposited within the Bauxite Residue Disposal Area (BRDA) located to the south-west of the plant. The BRDA covers an area of approximately 184 hectares (ha). A Salt Cake Disposal Cell (SCDC) is also located within the BRDA. The SCDC is an engineered cell that stores the salt cake hazardous waste created from removing the organic impurities when the bauxite is dissolved. The Project site plan is shown on **Figure 1.1.**

The proposed development consists of works to the BRDA comprising of an expansion to increase its disposal capacity to accommodate additional bauxite residue arising from the continued operation of the permitted alumina plant located on the wider AAL facility. The proposed increase in disposal capacity to the BRDA will result in a proposed increase in height of c.12m above the currently permitted stage 10 level (c. 32m OD) to a final stage 16 level (c. 44m OD). No increase to the existing footprint of the BRDA is proposed.

The proposed method of raising the BRDA will be the upstream method, consistent with the construction methodology for the current BRDA and involves the construction of rock fill embankments (Stages), offset internationally, and founded on the previously deposited and farmed bauxite residue, in 2 m high vertical lifts. The overall stack is raised systematically as the stages are filled with bauxite residue, farmed, carbonated, and compacted, prior to deposition of the next layer.

Additional works proposed as part of the application include the following:

- A vertical extension to the existing SCDC to accommodate further disposal of salt cake resulting in an increase in height of c.2.25m. The SCDC is located within the BRDA. A description of the SCDC and its function is provided in Chapter 2 of the Environmental Assessment Impact Report (EIAR).
- An extension of the existing borrow pit, located to the east of the BRDA, is also proposed. This extension proposes to increase the footprint of the borrow pit from c.4.5ha to c.8.4ha. This expansion will provide an additional 380,000m3 of rock fill material which is needed to satisfy the requirements of the construction and operation of the BRDA.
- The continued use of an existing stockpile area at the southeast of the subject site to store topsoil to satisfy the additional restoration requirements of the extended BRDA.
- Upgrades to the existing water management infrastructure to accommodate the BRDA development to Stage 16 which will also allow for greater Inflow Design Flood (IDF) capacity for the entirety of the BRDA.

Given that the proposed BRDA Raise and the proposed SCDC Raise sit entirely within the footprint of the existing BRDA, where reference is made to the BRDA within the following text, this will refer to both the BRDA and the SCDC areas unless otherwise stated. Please refer to Chapter 3.0 of the EIAR and the Engineering Design Report (provided as Appendix A of the EIAR) for a more detailed description of the proposed development.

WSP Canada Inc., in collaboration with Golder Associates Ltd. (a member of WSP Canada Inc.), has been retained to complete this Human Health Assessment ("HHA") in support of the EIAR. This HHA supports the human health assessment provided in Chapter 6 of the EIAR.

1.2 OBJECTIVES

This HHA is intended to provide a technical assessment that evaluates human health risks, if any, associated with exposures to potential emissions of bauxite residue and salt cake by-product from the Project.

The objectives of the HHA include the following:

- Evaluate the toxicity of the bauxite residue and salt cake by-products;
- Establish a "source-pathway-receptor" linkage to determine causal relationship between predicted exposures to bauxite residues and known health effects reported in publicly available epidemiological, occupational and/or animal toxicology studies. Priority will be given to primary literature and reviews prepared by credible sources including regulatory agencies and non-governmental organizations; and
- Characterize the health risks, if any, of nearby human populations associated with potential exposures to bauxite residues and salt cake by-products that may potentially be released from the Project.

Figure 1.1 Project Area (Source: Tom Phillips + Associates 2020)



2 PROJECT TEAM MEMBERSHIP

The project team has the necessary expertise to complete the HHA in a manner that meets international regulatory and technical requirements. The following provides a brief synopsis of the expertise and project experience of each team member in the completion of the HHA.

Theresa Repaso-Subang, DABT, ERT, QPRA - Lead Human Health Toxicologist

Ms. Theresa Repaso-Subang has 30 years of experience in environmental and human health toxicology and risk assessment. In 1995, Theresa received a certificate from Harvard School of Public Health in Risk Analyses and Risk Communications. Since 2004, Theresa has been a board-certified toxicologist with the American Board of Toxicology (DABT) and a European Registered Toxicologist (ERT) under the United Kingdom Registry of Toxicologists since 2015. As such, Theresa is bound by the codes of conduct of the American Board of Toxicology, Royal Society of Biology and British Toxicology Society. Theresa also received certification for the ethical conduct for research involving humans. Theresa is designated as a Qualified Person for Risk Assessments in the Province of Ontario and Saskatchewan in Canada. Theresa has been involved in the comprehensive reviews of toxicology data to support the development of ambient air quality standards on behalf of Health Canada, Ontario Ministry of Environment, Alberta Environment and Parks and World Health Organization. In support of permit applications, Theresa has been involved in the human health assessment of ambient air concentrations potentially impacted by ongoing and/or proposed infrastructure projects.

Ahmed Negm, M.Env.Sc. - Risk Assessor & Technical Resource

Mr. Ahmed Negm is a Risk Assessor with WSP's Toxicology & Risk Assessment Group located in Toronto, Ontario. He is a graduate of the University of Toronto and York University, with over five years of experience in environmental management. His experience specifically includes risk assessments and environmental site assessments. Ahmed specializes in providing support to human and ecological health RA projects, with responsibilities including data analysis and interpretation, exposure modelling (including vapour intrusion modeling of volatiles), toxicity assessments, risk characterization, development of risk management measures, report writing, and overall project coordination.

Lindsay Furtado, M.Sc. - Risk Assessor & Technical Resource

Ms. Lindsay Furtado is a Risk Assessor with WSP's Toxicology and Risk Assessment Group located in Kitchener, Ontario. Ms. Furtado holds a B.Sc. and M.Sc. in environmental toxicology. She has over 7 years of experience in the areas of environmental site assessment, and in human health and ecological risk assessment. These responsibilities have included records reviews, sample planning, sample collection, data and statistical analysis, conceptual site models, contaminant fate and exposure modelling, toxicity assessments, risk characterization, property specific standards, risk management measures, risk management plans, and report writing.

Yangfan Chen, M.Sc. – Risk Assessor & Technical Resource

Ms. Yangfan Chen is a Risk Assessor, with experience collaborating with the Canadian government, the Chinese government, universities and companies on human health risks projects and air pollution projects. Yangfan is currently a member of WSP's Toxicology and Risk Assessment Group located in Windsor, Ontario. She is supporting our clients on risk assessments, involved in data management and statistical analysis, exposure modelling and toxicology reviews. As a member of a project funded by Ontario Ministry of Economic Development, Job Creation and Trade (Canada) and the Natural Sciences and Engineering Research Council of Canada, Yangfan completed a Human Health Risk Assessment of $PM_{2.5}$. She is proficient at human health risk assessment, data interpretation and management, and environmental modelling. She is fluent in Mandarin.

3 OVERVIEW OF HEALTH RISK ASSESSMENT APPROACH

Risk assessment provides a quantitative description of the safety of a site. Generic regulatory guidelines do not consider site-specific conditions such as the types of people, wildlife, or fish present at a site. In addition, regulatory guidelines are not always available for all chemicals of potential concern (COPC). For these reasons, risk assessment is often used to identify COPCs and areas within a site that pose a human health risk. This information can be used to guide decisions about how risks can be managed, including if and where reduction of risks is required.

Risk assessment methods provide opportunities for the incorporation of public concerns and issues. This is particularly true for the problem formulation stage, as it is important that the right questions are asked, and the appropriate focus be given to subsequent stages in the assessment. Public involvement is also important in the risk reduction planning stage.

Risk assessment is widely used and recognized by regulators and the scientific community. Methods and guidance documents have been available for several years, and there is a growing body of experience in the development of risk reduction plans for proposed infrastructure projects. The risk assessment method used in this report is based on the following guidance documents:

- Guidance on the Management of Contaminated Land and Groundwater at EPA Licensed Sites, Ireland Environmental Protection Agency, Office of Environmental Enforcement, 2013;
- Risk Assessment in the Federal Government: Managing the Process, United States National Research Council, National Academy Press, Washington, D.C., 1983; and
- Risk Assessment Guidance for Superfund Volume 1: Human Health Evaluation Manual (Part A), U.S. Environmental Protection Agency, EPA/540/1-89/002, dated December 1989.

Risk assessment informs the decision-making process by providing the information to "match the effort with the risk". This means that the risk assessment findings inform the risk reduction plans so that they can be tailored to: (1) achieve an effective net reduction in risk; and (2) address the primary risk drivers whether these are the sources of contamination or specific pathways that link sources with receptors. Risk assessment also allows risks to be ruled out; that is, it identifies COPCs and pathways that do not represent a potential risk and can, therefore, be ruled out of consideration for risk reduction.

The source-pathway-receptor model is the foundation, the core framework for this HHA that establishes the basis for understanding how risks can be reduced or eliminated.

3.1 RISK ASSESSMENT FRAMEWORK

This HHA follows a widely recognized risk assessment framework, as illustrated in **Figure 3.1,** established by the National Research Council (NRC) and applied by US EPA and other international agencies. The four components of the risk assessment framework are: 1) Problem Formulation; 2) Exposure Assessment; 3) Toxicity or Effects Assessment; and 4) Risk Characterization. Each of the four components is described in the following sections.

3.1.1 PROBLEM FORMULATION

Problem formulation is used to focus the risk assessment on the chemicals, exposure pathways, and receptors that are most applicable to the Project. This focus is provided by using a fundamental principle in risk assessment that a risk cannot occur if there are no links between sources of exposure and people. As such, three elements are required: 1) sources of chemicals must be present; 2) receptors (e.g., people) must be present; and 3) exposure

pathways must exist between the source of the chemicals and the receptors (**Figure 3.2**). In the absence of any one of the three elements (source, pathway, or receptor), risks cannot occur. This source-pathway-receptor principle serves as the basis for this HHA for the Project and is also the basis for the remaining steps of the HHA.

The presence of all three elements in **Figure 3.2** does not necessarily indicate an unacceptable risk. Rather, source-pathway-receptor links indicate the potential for risk. This potential for risk is further investigated during problem formulation by a screening process. The screening process defines the following source-pathway-receptor linkages:

- Source: COPCs that occur at concentrations above regulatory guidelines and/or background levels; and
- Pathway: critical pathways that serve as the primary routes of exposure to COPC; and
- Receptor: receptors of concern that serve as representatives of human populations or communities because of their proximity to the Project, their sensitivity, and their anticipated exposure to emissions from the Project.

Figure 3.1 Risk Assessment Framework

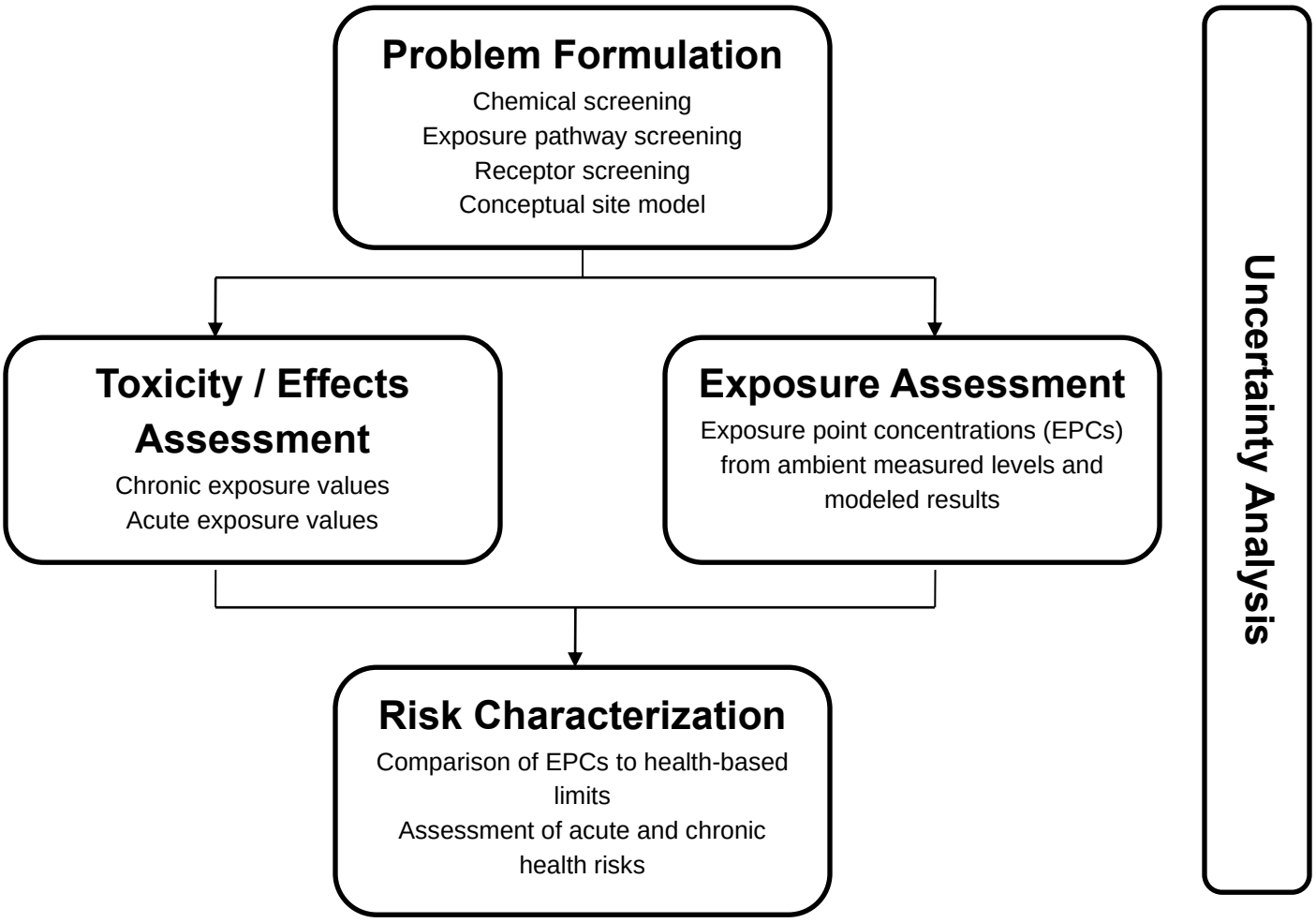
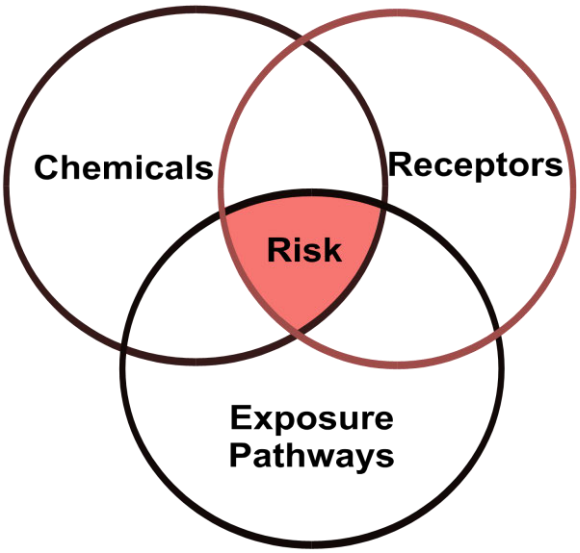


Figure 3.2 Three Elements of Risk



The methods used to screen chemicals, receptors, and pathways are briefly outlined below.

- Chemical screening: The objective of the chemical screening step is to focus on the chemicals of potential concern to be evaluated in the assessment. For this HHA, the COPCs are related to the by-products of the alumina processes including bauxite residues and salt cake. A literature search and review has been completed to assess bauxite residues and salt cake, and their constituents. This is further discussed in **Section 4**.
- Exposure pathway screening: The objective of exposure pathway screening step is to determine the potential routes by which human receptors could potentially be exposed to COPCs from the Project. The primary exposures evaluated in this HHA is inhalation of bauxite residues and salt cake (as particulates) and deposition of particulates.
- Receptor screening: The objective of the receptor screening process is to select a representative set of receptors who may be exposed to COPCs from the Project. For this HHA, young children who may be attending the closest school located 1.9 kilometres from the Project has been identified as a sensitive receptor. In addition, residents who are living approximately 0.5 km to the east in the vicinity of the Project have been identified as sensitive receptors.

Once the screening process is complete, the Problem Formulation continues with the development of a Conceptual Site Exposure Model of the source-pathway-receptor linkages that are expected to be the primary drivers of risk from the Project. Conceptual Site Exposure Model is a diagram or drawing that is used to present the results of the problem formulation.

- The problem formulation is complete when:
- COPCs are identified; and
- A Conceptual Site Exposure Model of source-pathway-receptor links have been developed.

The results of the problem formulation are carried forward to the next steps in the risk assessment.

3.1.2 EXPOSURE ASSESSMENT

An exposure assessment is completed for each chemical of potential concern identified in the problem formulation. For humans, exposure to chemicals is determined as a dose. This value is called the estimated daily intake (EDI) and is typically expressed as milligram (mg) of a chemical per kilogram (kg) of body weight per day (mg/kg-day). The EDI is calculated from site-specific concentrations of COPCs in air, the amount of time a receptor spends at the study area, and receptor-specific parameters such as body weight. For this HHA, it is conservatively assumed that

human receptors would spend their entire life in the study area and would be exposed to the concentrations of COPCs predicted in that area.

3.1.3 TOXICITY OR EFFECTS ASSESSMENT

The toxicity or effects assessment provides the basis for evaluating what is an acceptable exposure and what level of exposure may adversely affect human health. This involves identification of the potentially toxic effects of chemicals and determination of the dose that a receptor can be exposed to without experiencing unacceptable effects. This value is called the toxicity reference value (TRV) and is expressed as mg of a chemical per kg of body weight per day (mg/kg-day).

3.1.4 RISK CHARACTERIZATION

The final step in a risk assessment, referred to as risk characterization, involves comparing the estimated exposure to the TRV. The exposure ratio (ER) values for each COPC are calculated as the ratio of the estimated exposure (based on the exposure assessment) to the TRV (based on the toxicity assessment), according to the following equation:

$$ER = \frac{EDI}{TRV}$$

Where:
ER = exposure ratio;
EDI = estimated daily intake; and
TRV = toxicity reference value based on dose or daily intake.

The ER indicates whether the amount of a COPC taken in by people is greater than the amount of the COPC below which there would be essentially no risk of adverse health effects or no unacceptable risk of cancer (i.e., if the ER is less than 1 it is extremely unlikely that adverse health effects would occur). If the ER is greater than 1 (i.e., the exposure amount is greater than the threshold amount), the possibility of adverse effects cannot be ruled out and further consideration may be warranted.

Carcinogenic metals, in theory, do not exhibit threshold-response behaviour. Rather, even at low doses, there is some risk of genetic damage, although nature provides ways of repairing this to some extent. Human health effects for arsenic, a COPC that is known or suspected to cause cancer, were evaluated using the Incremental Lifetime Cancer Risk (ILCR). The ILCR is the increased risk attributed to exposure, above and beyond background cancer risks caused by genetics, lifestyle, and other non-chemical factors. The ILCR was calculated using the following equation:

$$ILCR = EDI \times SF$$

Where:
ILCR = Incremental Lifetime Cancer Risk;
EDI = Estimated Daily Intake (mg/kg-d); and
SF = Slope Factor $(mg/kg\text{-}d)^{-1}$.

To evaluate the acceptability of environmental exposures to carcinogenic substances, regulatory agencies (such as World Health Organization, US Environmental Protection Agency (EPA) and Health Canada) have established that an incremental increase in cancer incidence of 1 in 100,000 is essentially negligible. Irish EPA relies on the United Kingdom's Contaminated Land Exposure Assessment (CLEA) model, which applies a cancer risk of 1 in 100,000 as an acceptable target risk. The Irish Cancer Society (Cancer statistics | Irish Cancer Society, 2020) states that approximately 45,753 people in Ireland will develop cancer each year comprising of both invasive and non-invasive tumours. As such, the lifetime probability of developing cancer in Ireland is approximately 46% (a risk level of 46,000 in 100,000). Thus, an incremental cancer risk of 1 in 100,000 increases a person's lifetime cancer risk from 0.46000 to 0.46001. This increase would be undetectable using available epidemiological data and statistics, particularly in smaller populations that may reside near the Project.

4 PROBLEM FORMULATION

The problem formulation section of the HHA is the first step in the assessment that lays out the source-pathway-receptor linkage based on possible interactions of Project-related emissions and their interactions with human receptors who are present near the Project. This stage of the HHA describes the chemical screening, the receptor screening, and the exposure pathway screening to identify the chemicals of potential concern, human receptors of concern and exposure pathways to be evaluated further in the HHA.

4.1 CONTAMINANTS OF POTENTIAL CONCERN

This section describes how chemicals of potential concern (COPCs) are screened for further evaluation in this HHA. This section first discusses the primary COPCs including bauxite residue and salt cake, and the findings of the literature review that may be relevant for the Project. The constituents of the primary COPCs are discussed in more detail in Section 4.1.2 including detailed breakdown of the bauxite residue and salt cake.

4.1.1 ALUMINA PROCESS BY-PRODUCTS

The contaminants of concern for this assessment include the solid waste by-products of the alumina processes, namely bauxite residues and salt cake. Farmed bauxite residue is the terminology applied to describe bauxite residue which has undergone a process of partial neutralisation. Within the Alumina Industry bauxite residue may also be termed red mud. Given that bauxite residues and salt cake solid waste by-products are mixtures of chemicals, a literature search and review was completed to determine the available studies related to the toxicology and associated health effects from exposures to solid waste mixtures.

Using “bauxite residue” as key words for the literature search, the findings of the publication search and review are summarized as follows:

- Three (3) comprehensive reviews on bauxite residue were identified.
- These comprehensive reviews discuss waste management and not toxicology, human or environmental health associated with bauxite residue.
- The findings of the literature review are summarized in **Appendix A, Table A-1**.

Using “aluminium”, “bauxite dust” and “red mud” as key words for the literature search, the findings of the publication search and review are summarized as follows:

- Twenty-eight (28) studies that contained one or a combination of the above noted key words were identified pertaining to environmental impacts, occupational and human health risks.
- Of these studies, eight (8) studies were considered potentially relevant as they involved laboratory animal or human health findings related to bauxite residue as an industrial solid waste.
- The remaining studies were related to occupational exposures to bauxite mining and smelting operations. These studies involved exposures that were considered not relevant to the Project due to differences in operational activities, exposure intensity and difference in by-product composition. As such, these studies were not included in this assessment.
- There were no studies identified for salt cake.
- The findings of the literature review are summarized in **Appendix A, Tables A-2 and A-3** using “aluminium”, “bauxite residue”, “red mud” and “health risks” as key words in the literature search.

4.1.1.1 *WASTE CHARACTERIZATION OF BAUXITE RESIDUE*

The farmed bauxite waste characterization was completed in accordance with Annex II of the Extractive Waste Directive that stated, “*classification of the waste shall be according to the relevant entry in Directive 2000/532/EC*

with particular regard to its hazardous characteristics." The following methodology was applied to classify the farmed bauxite waste:

- Is the waste a 'Special Waste' subject to its own specific legislative provisions and therefore excluded from the scope of general Hazardous Waste legislation e.g., radioactive waste or decommissioned explosives. *Note: While bauxite residue disposal is primarily legislated via the Extractive Waste Directive 2006/21/EC, its waste classification follows the Hazardous Waste legislation.*
- Is the Waste already coded/classified in the EU 'List of Wastes'? *Note: Regarding bauxite residue there are two possible codes, one being hazardous and the other being non-hazardous. Thus, an assessment of each bauxite residue type from each Alumina Refinery BRDA is required to determine which code on the official EU 'List of Wastes' should be applied to the bauxite residue in question.*
- Determine the detailed composition of the waste mixture down to 0.1% concentration. *Note: It is necessary to identify the specific compounds present in the waste rather than employ elemental analysis.*
- Determine the contribution to Hazardous Property of each compound present in the waste.
- For each compound present in the waste identify if it is classified as dangerous i.e., is there an associated Risk phrase and Hazardous Property (HP) associated with that compound?
- For each HP (there are 15 potential HPs in total) sum of all percent compositions of compounds that contribute to the HP in question.
- Determine if the summation of the % compositions contributing to any specific HP causes the waste to exceed the threshold for that HP. If so, the bauxite residue would then be classified as having that HP and must be classified as hazardous due to the HP in question unless direct HP testing confirms that the waste is not hazardous.

The report detailing the non-hazardous classification of farmed bauxite residue and supporting laboratory analyses are provided in **Appendix B.**

The report summarises an assessment of AAL farmed bauxite residue which employs the following legislation:

1. EU Waste Framework Directive (2008/98/EC),
2. Commission Decision of 18 December 2014 amending Decision 2000/532/EC on the list of waste pursuant to Directive 2008/98/EC of the European parliament and of the Council (2014/955/EEC),
3. Commission Regulation (EU) No 1357/2014 of 18 December 2014, replacing Annex III to Directive 2008/98/EC of the European Parliament and of the Council on waste and repealing certain Directives,
4. Council Regulation (EU) 2017/997 of 8 June 2017 amending Annex 111 to Directive 2008/98/EC of the European Parliament and of the Council as regards the hazardous property HP 14 "Ecotoxic", and
5. Extractive Waste Directive (2006/21/EC). and the Extractive Waste Directive (2006/21/EC).

The report concludes that the summation of the hazard statement codes for each compound present in farmed bauxite residue shows no threshold is exceeded for any of the hazard properties.

In addition, the European Commission ruling, pertaining to Petition 0010/2006 by Patrick Culhane on behalf of Cappagh Farmers Support Group on the waste characterisation for the AAL Plant is also provided in **Appendix B**. This document summarizes the petitioner's concerns related to the AAL plant and the actions of the Irish EPA in allowing and facilitating the plant's alleged breaches of environmental law. The European Commission investigated the actions of the Irish EPA and other authorities and, concluded that they have not identified a breach of EU environmental law regarding the operation of the AAL plant.

4.1.1.2 *PHYSICO-CHEMICAL PROPERTIES*

Czovek (2011) and Gelencser *et al* (2011) characterized the physical properties and chemical composition of respirable fugitive dusts following an accidental collapse of the red mud containing reservoir on October 4, 2010,

whereby a highly alkaline red mud sludge was discharged into agricultural and residential lands near Ajka in Hungary.

The chemical composition of red mud samples included major elements such as iron and aluminium (particularly from hematite, cancrinite, calcite, and hydrogarnet) followed by calcium, silicon, titanium, potassium, and magnesium (Gelencser *et al*, 2011; Czovek, 2011). Other elements such as cesium, chromium, lanthanum, manganese, nickel, neodymium, scandium, thorium, uranium, vanadium, and zirconium are present at trace levels. The concentrations of measured metals (cadmium, cobalt, copper, and nickel) in the red mud dust were below the analytical detection limit (10 ppb).

The specific alkalinity of the PM10 fraction of resuspended dust was 3.7 μekv g-1 (Gelencser *et al*, 2011). The author concluded that the inhaled alkalinity from red mud dust is well below the recommended no-effect limit and the alkalinity of the red mud dust is unlikely to cause severe acute or chronic symptoms in healthy adults.

With respect to particulate size distribution, Gelencser *et al* (2011) reported that most of the mass of the red mud dust is concentrated at or above the aerodynamically equivalent diameter of 10 μm, with a smaller secondary mode around 4 μm. The number size distribution is dominated by particles with diameters of about 2 μm. The typical number size distribution of the red mud aerosol exhibits a pronounced peak in the range between optical diameters of 3 and 8 μm. Given the dominant size fraction of the red mud dust, the author stated that the red mud dust would primarily be deposited in the upper respiratory tract and can cause irritation in that region of the airway as well as irritation of the eyes (Gelencser *et al*, 2011). Also, particles are generally irregularly shaped with a coarse surface that might facilitate the adhesion of these particles on the airway epithelium (Czovek, 2011). Eye irritation was reported by residents of the affected area and workers involved in the cleanup in the weeks immediately following the accidental spill in Hungary (Czovek, 2011). The author did not discuss the length of time before the eye irritation cleared nor did the author report necessary treatments, if any.

Gelencser *et al* (2011) concluded that depending on meteorological conditions and dryness of the red mud, respirable alkaline particles could be emitted into ambient air. Depending on the dryness of the red mud, there is a high resuspension potential and alkalinity of the dust may cause irritation of the upper respiratory tract and eyes. The authors (Gelencser *et al*, 2011; Czovek, 2011) concluded that based on its size distribution and composition, the red mud dust appears to be less hazardous to human health than urban particulate matter.

4.1.1.3 *SKIN CORROSIVITY*

Four samples of farmed bauxite residue (collected from Q2 2019, Q4 2019, Q3 2020 and Q4 2020) and three samples of farmed red mud (collected from February 22, 2015) from the AAL facility were tested for skin corrosivity in humans. Skin corrosivity tests were completed in accordance with Organisation for Economic Cooperation and Development (OECD) Test Guideline 431 that addresses the human health endpoint skin corrosion by using *in vitro* test methods involving reconstructed human epidermis that closely mimics the properties of the upper parts of the human skin (i.e., the epidermis) (OECD 431, 2019).

Skin corrosion refers to the production of irreversible damage to the skin manifested as visible necrosis (defined as a form of cell injury leading to premature cell death) through the epidermis and into the dermis, following the application of a test chemical, as defined by the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (GHS).

All *in vitro* studies concluded that bauxite residue samples were classified as non-corrosive. Test results are provided in **Appendix C**.

4.1.1.4 *EYE IRRITATION*

Four samples of farmed bauxite residue (collected from Q2 2019, Q4 2019, Q1 2020 and Q4 2020) from the AAL facility were tested for ocular irritation tests in accordance with OECD Test Guideline 438. The OECD Test Guideline 438 is an isolated chicken eye test method for identifying: i) chemicals inducing serious eye damage and ii) chemicals not requiring classification for eye irritation or serious eye damage. OECD Test Guideline 438 is an *in vitro* test method that can be used to classify substances as causing serious eye damage (UN GHS Category 1) or as not requiring classification (UN GHS No Category). This test method uses eyes collected from chickens obtained

from slaughterhouses. The eye is surgically removed and mounted in an eye holder with the cornea positioned horizontally. The test substance and negative/positive controls are applied to the cornea (OECD 438, 2018).

Ocular corrosion and irritation are measured by a qualitative assessment of opacity (damage to epithelium based on fluorescence retention), quantitative measurement of swelling and a qualitative evaluation of macroscopic morphological damage to the surface. The endpoints are evaluated separately to generate an Isolated Chicken Eye (ICE) class for each endpoint, which are then combined to generate an Irritancy Classification for each test substance.

All *in vitro* studies concluded that bauxite residue samples were classified as non-irritant (UN GHS Classification: No Category). Test results are provided in **Appendix C**.

Three samples of farmed bauxite residue (collected from Q2 2016) were tested for acute eye irritation tests in accordance with OECD Test Guideline 405. The OECD Test Guideline 405 is an *in vivo* test using live rabbits intended to identify eye irritation and serious eye damage potential of chemicals. This method provides information on health hazard likely to arise by applying the test substance in a single dose in the conjunctival sac of one eye of each animal. The other eye, which remains untreated, serves as a control. The duration of the observation period is carried out to sufficiently evaluate the magnitude and reversibility of the effects observed. The eyes of the test animals are examined at 1, 24, 48, and 72 hours after test substance application. The ocular irritation scores are then evaluated in conjunction with the nature and severity of lesions, and their reversibility or lack of reversibility.

Following 1-hr of application to rabbit eye mucosa, all three samples of bauxite residue caused conjunctival effects to rabbit eye mucosa which were fully reversible within 72-hrs. All in vivo studies concluded that bauxite residue does not require classification as an eye irritant. Test results are provided in **Appendix C**.

4.1.2 COMPOSITION OF BAUXITE RESIDUE AND SALT CAKE

Given that bauxite residues and salt cake waste by-products are mixtures and due to their limited (or absent) toxicology data, a literature search and review was completed for their constituents.

AAL commissioned testing of the bauxite residue to determine its composition and classification, the results of this testing are summarised in **Table 4.1** for bauxite residue and **Table 4.2** for salt cake. All constituents were identified as chemicals of potential concern (or COPCs) and they were carried forward for further assessment in the HHA, with exception of those constituents that were listed as "Generally Recognized as Safe" ("GRAS") by the US Food and Drug Administration (FDA). Those substances listed as GRAS have been concluded to have "***no evidence in the available information …that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future***" (US FDA, 2018). Zinc oxide has been assigned as Type 2, on the basis that "*there is no evidence in the available information … that demonstrates a hazard to the public when it is used at levels that are now current and, in the manner, now practiced. However, it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard."* Given this uncertainty, zinc oxide has been identified as a COPC for further evaluation in this HHA.

Salt cake is a mixture of organic and inorganic impurities which originate from the naturally occurring raw material, bauxite. These organic impurities are removed in a deep evaporation and crystallisation area. A side stream of liquor is evaporated to twice its initial caustic concentration followed by cooling to crystallise out a Salt cake slurry that is filtered to produce a moist cake that is then stored in a dedicated cell in the BRDA. Salt cake is hazardous because of the caustic content which cannot be washed from the salt cake, as doing so would dissolve sodium oxalate, which is soluble in hot water.

Constituents of bauxite residue and salt cake that were listed by US FDA as GRAS and were screened out from further assessment included moisture, Bayer sodalite, Gibbsite, Quartz, Sodium carbonate (baking soda), Carbonate apatite, Sodium bicarbonate (baking soda), Sodium aluminate, Sodium hydroxide, Magnesium oxide, and potassium carbonate. The constituents of bauxite residue and salt cake that were screened out from further evaluation in the HHA total 33.5% and 61.5% of the total weight percentage, respectively. It is noted that the moisture content in bauxite residue and salt cake constitute 21.9% and 44%, respectively.

Table 4.1 Summary of Bauxite Residue Composition

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC?
FULL CHEMICAL ANALYSIS							
Moisture		Free H2O	21.9				No
Aluminium Goethite	1310-14-1	(Fe,Al)2O3. H2O	20.9	*		No	**Yes**
Hematite (Iron Oxide)	1317-60-8	Fe2O3	18.75	*		No	**Yes**
Calcium Cancrinite	12172-98-4	3(Na2O.Al2O3.2SiO2)2CaCO3	12.15	*		No	**Yes**
Bayer Sodalite (Silicic acid, Aluminium sodium salt)	1344-00-9	3(Na2O.Al2O3.2SiO2.2H2O)0.8 Na2CO3.0.2Na2SO4	5.35	*		Yes	No
Gibbsite (Aluminium hydroxide)	21645-51-2	Al2O3.3H2O	4.85	H319	Causes serious eye irritation	Yes	No
Perovskite (Calcium titanium trioxide)	12049-50-2	CaTiO3	4.1	*		No	**Yes**
Anatase and Rutile (Titanium dioxide)	131770-0/ 13463-67-7	TiO2	4.1	H332 H319 H335 H315	Harmful if inhaled Causes serious eye irritation May cause respiratory irritation Causes skin irritation	No	**Yes**
Hydrogarnet	68131-78-8	3CaO.Al2O3.SiO2.4H2O	2.95	*		No	**Yes**

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC?
Boehmite (Aluminium oxide hydroxide)	1318-23-6	Al2O3.H2O	2.15	*		No	**Yes**
Quartz (Silica; Silicon Dioxide)	14808-60-7	SiO2	0.7	H372 H373	Causes damage to organs May cause damage to organs	Yes	No
Sodium Carbonate (Disodium carbonate)	497-19-8	Na2CO3	0.31	H319	Causes serious eye irritation	Yes	No
Zircon (Zirconium silicate)	10101-52-7	ZrSiO4	0.3	H332 H319 H335 H315	Harmful if inhaled Causes serious eye irritation May cause respiratory irritation Causes skin irritation	No	**Yes**
Carbonate Apatite (Calcium carbonate)	471-34-1	5.2CaO.0.8Na2O.2.5CO2.P2O5	0.2	H319	Causes serious eye irritation	Yes	No
Gypsum (Calcium sulfate dihydrate)	10101-41-4	CaSO4.2H2O	0.15	*		No	**Yes**
Sodium Sulphate	7757-82-6	Na2SO4	0.075	*		No	**Yes**
Sodium Bicarbonate (Sodium hydrogen-carbonate)	144-55-8	NaHCO3	0.045	H315 H319	Causes skin irritation Causes serious eye irritation	Yes	No
Sodium Fluoride	7681-49-4	NaF	0.02	H300 (cat 2) H315 H319	Fatal if swallowed Causes skin irritation Causes serious eye irritation	No	**Yes**

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC?
Sodium Aluminate **(Aluminium sodium oxide)**	11138-49-1	NaAl(OH)4	0.005	H290 H314	May be corrosive to metals Causes severe skin burns and eye damage	Yes	No
Sodium Hydroxide	1310-73-2	NaOH	0	H314	Causes severe skin burns and eye damage	Yes	No
TRACE METALS							
Chromium Trioxide	1308-38-9	Cr2O3	0.2	*		No	**Yes**
Vanadium Pentoxide	1314-62-1	V2O5	0.2	H302 H332 H318 H341 H361 H335 H372 H411	Harmful if swallowed Harmful if inhaled Causes serious eye damage Suspected of causing genetic defects Suspected of damaging fertility or the unborn child May cause respiratory irritation Causes damage to organs Harmful if inhaled	No	**Yes**
Magnesium Oxide	1309-48-4	MgO	0.12	*		Yes	No
Cerium Oxide	1306-38-3	CeO	0.02	*		No	**Yes**
Potassium Carbonate	584-08-7	K2CO3	0.03	H302 H335 H315 H319	Harmful if swallowed May cause respiratory irritation Causes skin irritation Causes serious eye irritation	Yes	No
Manganese Oxide	1344-43-0	MnO	0.035	*		No	**Yes**

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC?
Gallium Trioxide	12024-21-4	Ga_2O_3	0.0085	*		No	**Yes**
Arsenic Trioxide	1327-53-3	As_2O_3	0.01	H300 H314 H350 H400 H410	Fatal if swallowed Causes severe skin burns and eye damage May cause cancer Very toxic to aquatic life Very toxic to aquatic life with long lasting effects	No	**Yes**
Niobium Pentoxide	1313-96-8	Nb_2O_5	0.014	H315 H319 H335	Causes skin irritation Causes serious eye irritation May cause respiratory irritation	No	**Yes**
Zinc Oxide	1314-13-2	ZnO	0.005	H410	Very toxic to aquatic life with long lasting effects	2	**Yes**
Lead oxide	1317-36-8	PbO	0.007	H302 H332 H360 H373 H410	Harmful if swallowed Harmful if inhaled May damage fertility or the unborn child May cause damage to organs Very toxic to aquatic life with long lasting effects	No	**Yes**
Yttrium Trioxide	1314-36-9	Y_2O_3	0.0095	H315 H335	Causes skin irritation May cause respiratory irritation	No	**Yes**
Strontium Oxide	1314-11-0	SrO	0.0095	H314	Causes severe skin burns and eye damage	No	**Yes**

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC?
Copper Oxide	1317-38-0	CuO	0.004	H400 H412	Very toxic to aquatic life Harmful to aquatic life with long lasting effects	No	**Yes**
Thorium Oxide	1314-20-1	ThO	0.01	H301 H311 H331 H350 H373	Toxic if swallowed Toxic in contact with skin Toxic if inhaled May cause cancer May cause damage to organs	No	**Yes**

Table 4.2 Summary of Salt Cake Composition

COMPOUND	CAS NO.	FORMULA	WEIGHT (%)	HAZARD STATEMENT CODE		US FDA GRAS (YES/NO?)	COPC
FULL CHEMICAL ANALYSIS							
Moisture		H2O	>41 to <46% (44% average)				No
Sodium Oxalate	62-76-0	$Na_2C_2O_4$	20.9	H302 H312	Harmful if swallowed Harmful in contact with skin	No	**Yes**
Aluminium Oxide	1344-28-1	Al_2O_3	18.75	None		No	**Yes**
Sodium Hydroxide	1310-73-2	NaOH	12.15			Yes	No
Sodium Carbonate	497-19-8	Na_2CO_3	5.35			Yes	No

4.1.2.1 *PHYSICO-CHEMICAL PROPERTIES*

The following agencies were consulted (in order of priority) with respect to available physical and chemical properties for constituents of bauxite residue and salt cake:

- ECHA's Database for REACH Registered Substances (https://echa.europa.eu/information-on-chemicals/registered-substances);
- OECD eChemportal (https://www.echemportal.org/echemportal/index.action and OECD's Work on Co-operating in the Investigation of High Production Volume Chemicals - List of all chemicals);
- International Chemical Safety Cards (www.ilo.org/dyn/icsc/showcard.display);
- Agency for Toxic Substance and Disease Registry (Agency for Toxic Substances and Disease Registry (cdc.gov); and
- Hazard Substance Data Bank (https://www.toxnet.nlm.nih.gov/newtoxnet/hsdb.htm).

Table 4.3 summarizes the available physico-chemical properties for constituents of bauxite residue and salt cake. Water solubility and log K_{ow} are important parameters that affect bioavailability of a substance in environmental media; thereby influencing its toxicity. Substances with very low water solubilities are likely to be less bioavailable in the environment. Note that many of the constituents of bauxite residue and salt cake are oxides and are insoluble in water with some slightly soluble. Constituents that are hydroxides have limited solubility in water. There are no available log K_{ow} for constituents of bauxite residue and salt cake.

4.1.3 NATURALLY OCCURING RADIOACTIVE MATERIAL (NORM)

Naturally occurring radioactive material (NORM) is found in the environment that contains radioactive elements of natural origin. Two sources of NORM are present at the Site as discussed below.

- The Radon Map for Ireland (Radon map | Environmental Protection Agency (epa.ie)) indicates that the Proposed Development is located in an area where between 1% and 5% of homes are estimated to be above the radon reference level (reflecting the nature of the underlying bedrock geology). The majority of the Study Area has the same radon reference level as the Site area. A small area in the east of the Study Area has a higher radon reference level where between 10% and 20% of homes in the 10 km grid are estimated to be above the reference level. The area south of the estuary also has a reference level which is higher than the Site area level with between 5% and 10% of homes likely to show exceedances in radon levels.
- In addition to naturally occurring radon in the bedrock, mineral raw materials such as bauxite exhibit natural radioactivity which is slightly above the average level in the earth's crust. In bauxite, both thorium 232 (Th-232) and uranium 238 (U-238) are present in measurable amounts. The EPA is currently the competent Authority in Ireland for dealing with regulatory, monitoring, and advisory responsibilities in matters pertaining to ionising radiation and radioactive contamination in the environment. Formerly, the Radiological Protection Institute of Ireland (RPII) was the competent Authority. The RPII has previously surveyed the Site and assessed the facility, raw materials (bauxite) and bauxite residue for NORM properties as part of the industry-specific radiological assessment undertaken for four (4) large industries operating in Ireland, dealing with NORM, which were prioritized to determine the level of radiation to which workers and members of the public were potentially exposed because of their work practices (RPII 2008). The results of the gamma spectrometry analysis of the samples collected by the RPII at the AAL facility are replicated in below, along with published data from similar facilities in other countries for comparison.

Activity concentrations for both Th-232 and U-238 decay series were detected and found to be in radioactive equilibrium in the bauxite residue. All measured activity concentrations were found to be below the European Commission (EC) and the International Atomic Energy Agency (IAEA) indicative recommended exclusion / exemption values for NORM materials. Below these concentrations, the radiation dose received by a worker or a member of the public dealing with this type of material is unlikely to exceed 300 microSieverts (mSv) per year. The threshold for an effective dose to workers or members of the public being > 1,000 mSv per year.

Figure 4.1 Radionuclide activity concentrations (Bq / kg dry weight) in samples collected at the AAL BRDA and compared with other published data (RPII 2008)

Reference and material	U-238 (maximum)	Th-232 (maximum)	U-235
This study			
Bauxite slurry	140	120	< 10
Scale top digester	250	260	20
Scale decanter	40	40	< 10
Red sand	150	170	7
Red mud	240	460	7
Liquid effluent (Bq/l)	3	0.3	< 10
[Von Philipsborn and Kühnast, 1992]			
Bauxite ore (Sierra Leone)Bauxite	30	30	
ore (Boké – Rep. Guinea)	130	160	
Bauxite ore (Queensland – Australia)	90	100	
Red mud (unspecified origin)	120	210	
[Beretka and Mathews, 1985]			
Red mud (Australia)	330	1130	
Red sand (Australia)	50	390	
[FNCA, 2005]			
Bauxite (Australia)	120	500	
Red mud (Australia)	400	1300	
[Cooper, 2005]			
Bauxite (Western Australia)	120-350	450-1050	
Red sand (Western Australia)	5-200	300-800	
Red mud (Western Australia)	150-600	1000-1900	
[European Commission, 2007]			
Red mud (Hungary)	250-570	260-400	7-11
Red mud (Bosnia and Herzegovina)	72	190	3
[European Commission, 2001a]			
Bauxite	50-500	50-500	
Red mud	260-540	340-500	
[Timmermans and van der Steen, 1996]			
Bauxite	500	400	
[IAEA, 2003]			
Bauxite	10-9000	35-1400	
Red mud	100-3000	100-3000	
[Marsh, 1991]			
Average in Irish soils	46	25	

RPII (2008) concluded that the low levels of NORM at the AAL plant comply with safe levels and below the threshold at which the facility would come within the scope of the Irish Regulations from a radiological point of view.

AAL undertook additional radioactive assessment of the farmed bauxite residue and process sand during 2021. Two (2) samples of farmed bauxite residue (composite samples from Q3 2020 and Q4 2020) and one sample (1) of process sand (composite sample produced during 2020) were tested via alpha- and gamma-spectrometry for the presence of thorium and uranium isotopes at the Socotec Laboratories in Oxfordshire, UK. One (1) thorium (Th-232) and three (3) uranium (U-234, U-235 and U238) decay series were detected.

Figure 4.2 Thorium Isotope Testing (AAL 2021) – Ac is the proxy for Th-232

Customer Reference	Laboratory Reference	Ac-228 (Bq kg^{-1})	Ra-224 (Bq kg^{-1})	Pb-212 (Bq kg^{-1})	Bi-212 (Bq kg^{-1})	Tl-208 (Bq kg^{-1})
Farmed Bauxite Residue Q3 2020	NA3281 *	313 ± 26	251 ± 57	314 ± 26	350 ± 51	101.0 ± 8.9
Farmed Bauxite Residue Q4 2020	NA3282 *	304 ± 25	267 ± 59	312 ± 25	329 ± 48	105.0 ± 8.9
Process Sand 2020	NA3283 *	164 ± 15	120 ± 45	151 ± 14	160 ± 39	47.3 ± 5.2

The direct daughter of ^{232}Th is ^{228}Ra which does not produce any significant gamma ray emissions. We can estimate the activity of ^{228}Ra from the daughter radionuclide ^{228}Ac but the ^{228}Ra may not be in equilibrium with the ^{232}Th. Radium-224 is a good estimator of the activity of ^{228}Th. The immediate daughter of ^{224}Ra is ^{220}Rn which is a gas and thus it is possible for ^{212}Bi & ^{212}Pb to underestimate the ^{228}Ra activity however that is not the case for these samples. Bismuth-212 decays to two possible radionuclides with only a 35.9% probability to ^{208}Tl and allowing for this it appears that there is reasonable equilibrium from ^{228}Ac through to ^{208}Tl.

Table notes

1. Results are presented as Bq.kg^{-1} of sample as received and are decay corrected to the sampling date provided.
2. Analyses and/or samples marked with an asterisk are not UKAS accredited under schedule 1252.
3. Uncertainties are rounded to 2 significant figures; results are rounded to the same precision.
4. For results below the Limit of Detection, the LoD is rounded up to 2 significant figures.
5. Detector calibrations are based upon homogeneous standard solutions. For quantification purposes the sample is assumed to be homogeneous.

Figure 4.3 Uranium Isotope Testing (AAL 2021)

Customer Reference	Laboratory Reference	U-234	U-235	U-238
	Reference Date:	31 August 2021		
Farmed Bauxite Residue Q3 2020	NA3281*	68 ± 11	5.5 ± 2.8	58 ± 10
Farmed Bauxite Residue Q4 2020	NA3282*	91.2 ± 8.5	5.0 ± 1.5	92.7 ± 8.6
Process Sand 2020	NA3283*	82.0 ± 9.7	4.0 ± 1.7	79.7 ± 9.6

Notes:

1. Results and/or samples marked with an asterisk are not UKAS accredited.
2. Results are presented as Bq.kg^{-1} of sample as received, relative to the reference date.
3. Uncertainties are quoted at 2 s.d. based on a total uncertainty budget.

A comparison of the 2008 and the 2021 results shows:

- Th-232 was present in the unfarmed bauxite residue at an average value of 460 Bq / kg in 2008 and was present in the farmed bauxite residue at an average value of 309 +/- 25 Bq / kg in 2020 (average of Q3 value of 313 and Q4 value of 304 for Ac-208).
- Th-232 was present in the process sand at an average value of 170 Bq / kg in 2008 and was present in the process sand at 164 +/- 15 Bq / kg in 2020.
- U-238 was present in the unfarmed bauxite residue at an average value of 240 Bq / kg in 2008 and was present in the farmed bauxite residue at an average value of 75 +/- 10 Bq / kg in 2020 (average of Q3 value of 58 and Q4 value of 93 for U-238).
- U-238 was present in the process sand at an average value of 150 Bq / kg in 2008 and at 80 +/- 10 Bq /kg in 2020.
- U-235 was present in the unfarmed bauxite residue and the process sand at average values of 7 Bq / kg in 2008 and was present in the farmed bauxite residue and process sand at average values of 5.3 +/- 2.8 Bq / kg (average of Q3 value of 5.5 and Q4 value of 5.0 for U-235) and 4 +/- 1.7 Bq / kg, in 2020, respectively.

The 2021 test results are either comparable to or slightly lower in comparison with previous RPII assessment. As such, the BRDA does not present a radiation hazard to the surrounding environment and is not considered further in the assessment. The analytical results are provided in **Appendix D**.

Table 4.3 Summary of Physical and Chemical Properties for Constituents of Bauxite Residue and Salt cake

CAS NO.	FORMULA	Molecular Weight	Physical State	Melting Point	Boiling Point	Solubility in water at 25°C	Thresholds (TLV/TWA)	Log Kow	Log Koc	Vapour Pressure	pH	Henry's Law Constant (if available)	Flammability	Explosives Limit	Other Sources
1310-14-1	(Fe,Al)2O3.H2O	88.85		NA		Immiscible (Data sheets)					5-7.5 (10 gm/250 ml) (Data Sheets)				https://datasheets.scbt.com/sc-252863.pdf
1317-60-8	Fe2O3	159.69	Solid (at 20°C and 1013 hPa)	1 565°C (at101325 Pa)	above 300°C	insoluble	8 hr Time Weighted Avg (TWA): 5 mg/cu m (respirable fraction)			NA	NA		Preliminary data exclude a mixture auto-flammability until 400°C.	non -explosive	Physical state, boiling point, vapour pressure, PH, flammability, explosive limit from ECHA REACH:https://echa.europa.eu/registration-dossier/-/registered-dossier/7586/4/4.
12172-98-4	3(Na2O.Al2O3.2SiO2)2CaCO3														no link
1344-00-9	3(Na2O.Al2O3.2SiO2.2H2O)0.8Na2CO3.0.2Na2SO4	202.14	FINE, WHITE, AMORPHOUS POWDER OR BEADS (PubChem), Physical state at 20°C and 1013 hPa: solid (ECHA REACH)	1 710°C (ECHA REACH)	NA	insoluble (PubChem); ca. 68 - ca. 79 mg/L (ECHA REACH)					6.5-10.5 (20% SLURRY)		NA (ECHA REACH)	Not explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15116/4/15
21645-51-2	Al2O3.3H2O	78.004	Solid	300 °C	Boiling point at 101 325 Pa: 2 980 °C	Insoluble (PubChem); Aluminium hydroxide is poorly soluble, with a water solubility of 0.00009 g/L at 20 °C. (ECHA REACH)	8 hr Time Weighted Avg (TWA): 1 mg/cu m, respirable fraction. TLV :			Vapor pressure, Pa at 20 °C:	Max. 10. (MSDS)		non flammable (ECHA REACH)	aluminium hydroxide is not considered to be explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15529/4/15 MSDS: https://www.cdhfinechemical.com/images/product/msds/183_234856393_AluminiumHydroxide-CASNO-21645-51-2-MSDS.pdf
12049-50-2	CaTiO3	135.94	solid	1 980°C (ECHA REACH)	The melting point of calcium titanate is >300°C (ECHA REACH)	0.3 mg/L at 25 °C				NA (ECHA REACH)	NA		not highly flammable (ECHA REACH)	non explosive (ECHA REACH)	
131770-0/ 13463-67-7	TiO2	79.866	Solid	3380 °F (decomposes) (NTP, 1992)/1855 °C/3326-3362°F	4532 to 5432 °F at 760 mm Hg; 2500-3000 °C (Weast, R.C. (ed.) Handbook of Chemistry and Physics. 69th ed. Boca Raton, FL: CRC Press Inc., 1988-	insoluble/ less than 1 mg/mL	8 hr Time Weighted Avg (TWA): 10 mg/cu m .			0 mm Hg at 68 °F Essentially	SUSPENSION IN WATER (1 IN 10) IS NEUTRAL TO LITMUS		Noncombustible; Not combustible (ICSC)		ICSC: https://www.ilo.org/dyn/icsc/showcard.display?p_card_id=0338

CAS NO.	FORMULA	Molecular Weight	Physical State	Melting Point	Boiling Point	Solubility in water at 25ºC	Thresholds (TLV/TWA)	Log Kow	Log Koc	Vapour Pressure	pH	Henry's Law Constant (if available)	Flammability	Explosives Limit	Other Sources
					1989., p. B-140)										
68131-78-8	3CaO.Al2O3.SiO2.4H2O					NA					NA				
1318-23-6	Al2O3.H2O	59.988	Dry Powder (Pubchem); Solid (ECHA REACH)	>300 °C thus NA (ECHA REACH)	NA(ECHA REACH)	NA(ECHA REACH) insoluble in H2O (Chemical book)		NA (ECHA REACH)		NA (ECHA REACH)			non-flammable (ECHA REACH)		ECHA REACH:https://echa.europa.eu/registration-dossier/-/registered-dossier/15111/4/14 Chemical Book: https://www.chemicalbook.com/ProductChemicalPropertiesCB1212426_EN.htm
14808-60-7	SiO2	60.084	solid	1710 °C(Pubchem); 1610 °C (CESAR); 1610 °C (ICSC)	2230 °C	insoluble	8 hr Time Weighted Avg (TWA): 0.025 mg/cum, respirable fraction			10 mm Hg @ 1732 °C	NA		non-combustible	non-combustible(ICSC)	CESAR: http://www.ec.gc.ca/ese-ees/1EB4F4EF-88EE-4679-9A6C-008F0CBC191C/FSAR_B12%20-%2014464-46-1%20%26%2014808-60-7%20%28QC%29_EN.pdf ICSC:https://pubchem.ncbi.nlm.nih.gov/compound/24261#section=Chemical-and-Physical-Properties
497-19-8	Na2CO3	105.988	Dry Powder(Pubchem) ;Solid (ECHA REACH)	856 °C/851 °C(PubChem); 856 °C(ECHA REACH); 851 °C (ICSC)	Decomposes on heating by CO2 loss(Pubchem);Not possible to determine the boiling point of sodium carbonate. It decomposes above 400 centigrade to CO2 and Na2O thus making determination of a boiling point impossible (Echa REACH)	soluble in water (30.7 g/100 g)		NA		Negligible (ECHA REACH)	Aqueous solutions are strongly alkaline. At 25 °C, the pH of 1, 5 and 10 wt% sodium carbonate solutions are 11.37, 11.58 and 11.70, respectively. (PubChem); 10.33 (ECHA REACH)		non-flammable	non-explosive	ECHA REACH:https://echa.europa.eu/registration-dossier/-/registered-dossier/15432/4/15 ICSC:https://www.ilo.org/dyn/icsc/showcard.display?p_card_id=1135
10101-52-7	ZrSiO4	183.31	Solid			NA					NA				

CAS NO.	FORMULA	Molecular Weight	Physical State	Melting Point	Boiling Point	Solubility in water at 25ºC	Thresholds (TLV/TWA)	Log Kow	Log Koc	Vapour Pressure	pH	Henry's Law Constant (if available)	Flammability	Explosives Limit	Other Sources
471-34-1	5.2CaO.0.8Na2O.2.5CO2.P2O5	100.09	Dry Powder(Pubchem); Solid (ECHA REACH)	The melting point of calcium carbonate as aragonite is 825 °C and as calcite is 1339 °C. (ECHA REACH)	NA(ECHA REACH)	slightly soluble (0.1-100 mg/L)	TLV-TWA (Time Weighted Average):10 mg/m³ (inhalable particles), 3 mg/m³ (respirable particles)	NA		NA (ECHA REACH)	7 - 9 @ 20°C (MSDS)	0.00000000378 atm-m3/mole (Predicted by US EPA)	Not combustible.	Noncombustible Solid	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/16050/4/7 US EPA: https://cfpub.epa.gov/ecotox/explore.cfm?cas=471341 MSDS: https://www.fishersci.ca/store/msds?partNumber=AC192721000&productDescription=calcium-carbonate-99-biochemistry-acros-organics-2&language=en&countryCode=CA
10101-41-4	CaSO4.2H2O	172.17	Solid	100-150 °C		0.2g/100ml (very poor)	(inhalable fraction): 4 mg/m3; pregnancy risk group: C.			0 mm Hg (approx)	7 5% aq. solution (MSDS)		Not combustible	Not combustible	MSDS: https://www.fishersci.com/store/msds?partNumber=AA33301A1&productDescription=CLCM+SULFATE+DIHYDRATE+99%25+1KG&vendorId=VN00024248&countryCode=US&language=en
7757-82-6	Na2SO4	142.02	Dry powder/solid	884 °C(Pubchem)/ 800 °C (ECHA REACH)/ 884 °C(ICSC)		28.1 g/100 g(very good)		log Kow = -4.38 (est)			pH of a 5% solution = 9.0 (typical value)		Not combustible (ICSC)	not explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/13138/4/15 ICSC:https://www.ilo.org/dyn/icsc/showcard.display?p_card_id=0952
144-55-8	NaHCO3	84.007	Dry powder	Decomposes at 228° F		8.7g/100ml at 20 °C:					Between 8,0 and 8,6 (1 % solution)		Not combustible.	not explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/16157/4/15
7681-49-4	NaF	41.588	Solid dry powder	993 °C	1700 °C	4.3 g/100 ml	8 hr Time Weighted Avg (TWA): 2.5 mg/cu m.			1 mm Hg at 1971 °F; 5 mm Hg at 2167° F	7.4 (Freshly prepared saturated soln)		Not flammable	Not flammable	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/14274
11138-49-1	NaAl(OH)4	81.97	powder	32 °F (USCG, 1999)/1650 °C (ICSC)	239 °F at 760 mm Hg	Solubility in water: very good	8 hr Time Weighted Avg (TWA): 1 mg/cu m (Respirable fraction).				AQ SOLN IS STRONGLY ALKALINE		Not combustible.	Not combustible.	USCG: U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office./ICSC: https://www.ilo.org/dyn/icsc/showcard.display?p_version=2&p_card_id=0566
1310-73-2	NaOH	39.997	Dry powder	323 °C/318 °C	1388 °C	at 20 °C: 109 g/100ml (very good)	Ceiling Limit: 2 mg/cu m.			0 mm Hg (approx)	pH of a 0.05% wt/wt solution about 12; 0.5% solution about 13; 5% solution about 14		Not flammable	Not combustible.	
1308-38-9	Cr2O3	151.99	Dry powder	2435 °C	4000 °C	In water, 3.13 ug/L at 20 °C, pH 6; 2.96 ug/L at 20 °C, pH 8	8 hr Time Weighted Avg (TWA): 0.5 mg/cu m	NA (ECHA REACH)		Waived (ECHA REACH)	Trivalent chromium compounds are amphoteric		Not combustible	Not combustible	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15477/4/7
1314-62-1	V2O5	181.88	Dry powder	681 °C/690 °C	1750 °C (decomp)	0.07 g/100 g water	8 hr Time Weighted Average: 0.05 mg/cu m			Approximately 0 mm Hg at 68 °F	pH = 2.7, saturated aqueous solution at 20 °C		Not combustible.	Not combustible.	

CAS NO.	FORMULA	Molecular Weight	Physical State	Melting Point	Boiling Point	Solubility in water at 25ºC	Thresholds (TLV/TWA)	Log Kow	Log Koc	Vapour Pressure	pH	Henry's Law Constant (if available)	Flammability	Explosives Limit	Other Sources
							(inhalable fraction)								
1309-48-4	MgO	40.305	Solid	2825 °C/2800 °C	3,600 °C	86 mg/L at 30 °C	8 hr Time Weighted Avg (TWA): 10 mg/cu m (Inhalable fraction).			0 mm Hg (approx)	pH = 10.3 (saturated aqueous solution)		Not combustible.	Not combustible.	
1306-38-3	CeO	172.115	Dry powder (Pubchem)/Solid (ECHA REACH)	> 400 °C (ECHA REACH)	> 400°C (ECHA REACH)	< 0.123 µg/L at 20°C (ECHA REACH)				Data waiving (ECHA REACH)	between 6.01 and 6.41 (ECHA REACH)		not highly flammable (ECHA REACH)	non explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15783/4/3
584-08-7	K2CO3	138.205	Dry powder	899 °C/891 °C (PubChem)/891°C (ECHA REACH)	Decomposes	111 g/100 g water at 25 °C				Waived (ECHA REACH)	pH = 11.6 (aqueous solution)		Not combustible.	Not combustible.	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15221/4/7
1344-43-0	MnO	70.937	Dry Powder	1840 °C	above 300°C (ECHA REACH)	insoluble in water	8 hr Time Weighted Avg: 0.2 mg/cu			Waived (ECHA REACH)	NA		Non combustible	Non combustible	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/14280/4/4
12024-21-4	Ga2O3	187.44	powder	3236 to 3290 °F		No information available (MSDS)					No information available (MSDS)				MSDS: https://www.fishersci.ca/store/msds?partNumber=AA3210206&productDescription=gallium-iii-oxide-99-99-metals-basis-2&language=en&countryCode=CA
1327-53-3	As2O3	395.68/197.84 (AICIS)	powder (ECHA REACH)	313 °C (ECHA REACH)	460 °C (ECHA REACH)	very soluble (> 10000 mg/L)(ECHA REACH)	TLV: 0.01 mg/m3, as TWA (ICSC)			0.033 Pa (ECHA REACH)	no information available (MSDS)		non flammable (ECHA REACH)	non explosive	AICIS: https://www.industrialchemicals.gov.au/sites/default/files/Trivalent%20arsenites_Human%20health%20tier%20II%20assessment.pdf ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/14857/4/3 ICSC:https://www.ilo.org/dyn/icsc/showcard.display?p_card_id=0378 MSDS: https://www.alfa.com/en/msds/?language=EN&subformat=AGHS&sku=43488
1313-96-8	Nb2O5	265.81	Dry powder	1 512 °C (ECHA REACH)	NA	0.5 µg/L at 20 °C (ECHA REACH)		NA (ECHA REACH)			pH=8 (ECHA REACH)		non flammable (ECHA REACH)	non explosive	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/14981/4/9
1314-13-2	ZnO	81.4	Powder	1974 °C		0.00042 g/100 cu cm water at 18 °C (PubChem)/ 2.9 mg/L at 20 °C (ECHA REACH)				0 mm Hg (approx)	pH = 6.95 (American process zinc oxide); 7.37 (French process) (PubChem)/ 6.72 (uncoated)/ 6.75 (coated) (ECHA REACH)		Not combustible.	Not combustible.	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/16139/4/9

CAS NO.	FORMULA	Molecular Weight	Physical State	Melting Point	Boiling Point	Solubility in water at 25ºC	Thresholds (TLV/TWA)	Log Kow	Log Koc	Vapour Pressure	pH	Henry's Law Constant (if available)	Flammability	Explosives Limit	Other Sources
1317-36-8	PbO	223	Dry powder	887 °C	1470 °C/1472 °C	0.0504 g/L	8 hr Time Weighted Avg (TWA): 0.05 mg/cu m.	NA (ECHA REACH)		1 Pa at 724 °C; 10 Pa at 816 °C; 100 Pa at 928 °C; 1kPa at 1065 °C; 10 kPa at 1241 °C; 100 kPa at 1471 °C	Strong base		Non-combustible	Non-combustible	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15541/4/8
1314-36-9	Y2O3	225.81	Dry powder	above 400°C(ECHA REACH)	above 400°C(ECHA REACH)	0.7 mg/L at 20 °C (ECHA REACH)					No information available (MSDS)		non flammable (ECHA REACH)	non explosive(ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/14370/4/15 MSDS:https://www.fishersci.com/store/msds?partNumber=AA111822A1&productDescription=YTTM%28III%29+OXIDE+99.999%25+1KG&vendorId=VN00024248&countryCode=US&language=en
1314-11-0	SrO	103.62	Solid(ECHA REACH)	2 430 °C	NA(ECHA REACH)	7.63 g/L at 20 °C (ECHA REACH)					13.2 (ECHA REACH)		NA (ECHA REACH)	non explosive(ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/25528/4/9
1317-38-0	CuO	79.55	Dry powder	1326 °C	1026 °C	Practically insoluble in water	8 hr Time Weighted Avg (TWA): 0.2 mg/cu m	0.00000085 (ECHA REACH)		NA(ECHA REACH)	7 (50g/L aq. sol.) (MSDS)		NA (ECHA REACH)	NA (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/15443/4/1 MSDS: https://fscimage.fishersci.com/msds/05655.htm
1314-20-1	ThO	264.036	powder	3390 °C	4400 °C	Insoluble					no data available(MSDS)		Some of these materials may burn, but most do not ignite readily. Many have cardboard outer packaging; content (physically large or small) can be of many different physical forms.		MSDS: https://www.cdhfinechemical.com/images/product/msds/107_590237406_THORIUMOXIDECASNO1314-20-1MSDS.pdf
62-76-0	Na2C2O4	134	solid	The test item decomposes at 250 °C (ECHA REACH)	NA (ECHA REACH)	3.74 g/100g at 21.8°C (ECHA REACH)		-0.855 (ECHA REACH)		0 Pa (ECHA REACH)	Neutral in solution (MSDS)		Waived (ECHA REACH)	NA (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/28038/4/7 MSDS: https://fscimage.fishersci.com/msds/21450.htm
1344-28-1	Al2O3	101.961	white powder	2977 °C/3000 °C	2030 °C/2054 °C	Insoluble	8 hr Time Weighted Avg (TWA): 1 mg/cu m, respirable fraction			100 Pa at 2122 °C; 1 kPa at 2351 °C; 10 kPa at 2629 °C; 100 kPa at 2975 °C	9.4-10.1 at 20°C (MSDS)		Not combustible.	non explosive (ECHA REACH)	ECHA REACH: https://echa.europa.eu/registration-dossier/-/registered-dossier/16039/4/15 MSDS: https://beta-static.fishersci.com/content/dam/fishersci/en_US/documents/programs/education/regulatory-documents/sds/chemicals/chemicals-a/S25149.pdf

4.1.4 SUMMARY OF CONTAMINANTS OF POTENTIAL CONCERN

Bauxite residue is classified as "non-corrosive", "non-irritant to the eyes" and "non-hazardous". Salt cake is classified as hazardous. Given that the solid waste by-products are mixtures and due to their limited (or absent) toxicology data, the HHA identified the constituents of the bauxite residue and salt cake as COPCs. Except for those constituents that were listed as "Generally Recognized as Safe" ("GRAS") by the US FDA, the following COPCs are further evaluated in the HHA:

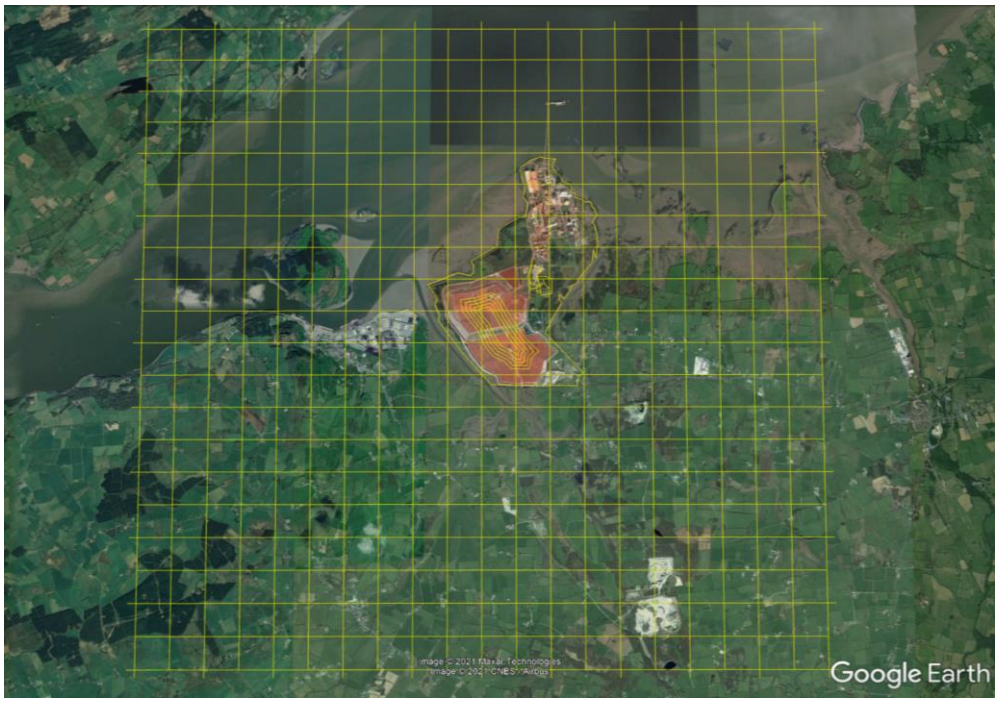
Table 4.4 Summary of Identified Contaminants of Potential Concern

CONTAMINANTS OF POTENTIAL CONCERN	CAS NO.
BAUXITE RESIDUE	
Aluminium Goethite	1310-14-1
Hematite (Iron Oxide)	1317-60-8
Calcium Cancrinite	12172-98-4
Perovskite (Calcium titanium trioxide)	12049-50-2
Anatase and Rutile (Titanium dioxide)	131770-0/ 13463-67-7
Hydrogarnet	68131-78-8
Boehmite (Aluminium oxide hydroxide)	1318-23-6
Zircon (Zirconium silicate)	10101-52-7
Gypsum (Calcium sulfate dihydrate)	10101-41-4
Sodium Sulphate	7757-82-6
Sodium Fluoride	7681-49-4
Chromium Trioxide	1308-38-9
Vanadium Pentoxide	1314-62-1
Cerium Oxide	1306-38-3
Manganese Oxide	1344-43-0
Gallium Trioxide	12024-21-4
Arsenic Trioxide	1327-53-3
Niobium Pentoxide	1313-96-8
Zinc Oxide	1314-13-2
Lead oxide	1317-36-8
Yttrium Trioxide	1314-36-9
Strontium Oxide	1314-11-0
Copper Oxide	1317-38-0
Thorium Oxide	1314-20-1
SALT CAKE	
Sodium Oxalate	62-76-0
Aluminium Oxide	1344-28-1

4.2 RECEPTORS OF POTENTIAL CONCERN

This HHA evaluated the source-pathway-receptor linkage within the Project Study Area defined in the Air Quality Impact Assessment (see Chapter 11 of the EIAR) (AWN, 2021). The Study Area is defined as the 10-kilometre (km) x 10 km box centered on the Project, as shown on Figure 4.4 below (adapted from Figure 1 from AWN, 2021).

Figure 4.4 Study Area for the HHA



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Project
Aughinish Alumina

Reference
21/12012AR01

Figure 1
Air Modelling Study Area (10km x 10km)
(UTM Coordinates)

The human receptors evaluated in the HHA were identified based on land use(s) within the Project Study Area. The human receptors associated with the identified land uses are intended to be inclusive of human populations including sensitive subpopulations such as children and residents. As such, the following human receptors were identified within the Project Study Area:

- **Schools** – Scoil Naisiunta Sheanain, a primary school with approximately 90 students, is the closest school located 1.9 km to the west of the BRDA. The HHA evaluated children, aged 5 to 13 years old, who are attending this school for a typical nine-hour day (including before and after school programs), five days per week, for 10 months (i.e., school year);
- **Workers** – Workers are considered adult teachers who work at the Scoil Naisiunta Sheanain primary school for a typical nine-hour work shift, five days per week, for 48 weeks of the year (i.e., assuming 4 weeks of vacation per year); and
- **Residential Community** –individuals who live in the residential communities near the Project.

The exposure modelling, described below in **Section 5**, considered that all above noted human receptors may be exposed to maximum impacts associated with ambient concentrations of identified COPCs that may be influenced by emissions from the Project. Potential exposure by human receptors was assumed to occur at the worst-case location at the Project boundary (i.e., fence line). This approach may be overly conservative if the likelihood of human presence is not accounted for in the risk characterization.

4.2.1 CHARACTERIZATION OF EXISTING COMMUNITY HEALTH

This subsection provides a description of the existing health of the community near the Project. The characterization of the existing community health serves as the baseline condition for which the environmental effects of the Project are predicted and assessed.

The following sources of information were used to gather health-related information pertaining to the existing health of the community near the Project, where available.

1. **2015 Health Profile for the City of Limerick and Limerick County** [Reference: Limerick County.pdf (lenus.ie)]

The report discusses four (4) principal disease groups including cancer, heart disease and stroke; respiratory disease; and injury and poisoning.

The hospital (age-standardized) discharge rate per 100,000 population between 2007-2011 for the four diseases was examined. The cancer rate for Limerick was lower than the Ireland rate (~ 1500 vs. 2500). For the three other disease categories, the Limerick rate was marginally higher than the Ireland rate.

The death rate per 100,000 for the four diseases as well as the death rate for those under 75 years (premature mortality) between 2007-2012 was examined. For all four disease types, the Limerick rate was higher than the Ireland rate. However, it should be noted that for heart disease & stroke as well as respiratory disease, Limerick (as well as Ireland as a whole) seem to be moving towards a steady decline.

The report also examined the following additional health metrics:

- Neonatal mortality (2012 data) per 1,000 live births: Limerick rate (3.4) vs Ireland rate (2.7);
- Infant mortality (2012 data) per 1,000 live births: Limerick rate (4.3) vs Ireland rate (3.5);
- Persons whose health is bad or very bad (based on 2011 self-health reporting census): Limerick (%) rate (1.3) vs Ireland (%) rate (1.5); and
- Cancer incidence (age standardized) rates (2011 data) for female and/or male skin cancer, melanoma, prostate cancer, breast cancer, colorectal cancer, and lung cancer: results showed that Limerick County has a higher than national incidence of female colorectal cancer. However, Limerick cancer incidences for all other cancer types are equal to average or below average in comparison to Ireland cancer incidence rates.

2. **2019 Health in Ireland, Key Trends 2019, Department of Health** [Reference: **Error! Hyperlink reference not valid.**]

This report summarizes key health trends on a national level from 2009 to 2019 including population growth, life expectancy and health status to profiles of the regional health areas. While the report does not summarise Limerick-specific health data, an overview of certain health indicators for different regions are provided.

The report states that life expectancy continues to improve in Ireland, with life spans increasing by 3 years and almost 2 years for male and female groups, respectively. Mortality rates have declined 10.5% since 2009. Age-standardized death rates for major causes of death such as cancers and circulatory system diseases have declined by 10% and 25%, respectively over the past ten years.

Lifestyle factors such as smoking, drinking, levels of physical activity and obesity continue to be health risk factors. However, inequalities in health are closely linked with wider social determinants including living and working conditions, issues of service access and cultural and physical environments.

3. **Ireland Central Statistics Office** [Reference: Data (cso.ie)]

The Central Statistics Office is the statistical agency responsible for gathering information related to economic, social, and general activities and conditions in Ireland. This agency collects and reports on the results of the National Census which is held every 5 years.

The Central Statistics Office provides the mortality rate and cause of death for Ireland and its counties. **Table 4.5** below summarizes the death rate per 100,000 population for both sexes related to several diseases for Limerick County in comparison to all other counties and regions.

Table 4.5 illustrates the following salient points:

- Death rate per 100,000, for both sexes, for many diseases for Limerick is **lower or equivalent to other counties** including all other malignant neoplasms, chronic lower respiratory diseases, complications of pregnancy, childbirth and puerperium, diseases of the digestive system, malignant neoplasm of cervix uteri, malignant neoplasm of colon, malignant neoplasm of kidney, malignant neoplasm of larynx, malignant neoplasm of lip, oral cavity & pharynx, malignant neoplasm of oesophagus, malignant neoplasm of prostrate, malignant neoplasm of skin, malignant neoplasm of stomach, other diseases of the circulatory system;
- Death rate per 100,000, for both sexes, for many diseases for Limerick is **marginally higher (less than two times)** than the death rates for other counties including acute myocardial infarction, all other malignant neoplasms, cancer of the trachea, bronchus and lung, cerebrovascular diseases, diseases of the circulatory system, diseases of the nervous system and the sense organs, diseases of the respiratory system, ischaemic heart disease, malignant neoplasm of bladder, malignant neoplasm of breast, malignant neoplasm of larynx and trachea, bronchus and lung, malignant neoplasm of liver and intrahepatic bile ducts, malignant neoplasm of lymph/hematopoietic tissue, malignant neoplasm of uterus, malignant neoplasm of ovary, malignant neoplasm of pancreas, malignant neoplasm of rectum and anus, malignant neoplasms, other diseases of the respiratory system, other heart disease, and tuberculosis;
- Death rate per 100,000, for both sexes, for diseases of the blood and blood forming organs, and immunological disorders for Limerick is **two times higher** than other counties; and
- The statistics provided corroborates the information detailed in the 2015 Health Profile. The data indicates that there is a **steady decline from 2009 to 2017**.

Table 4.5 Death Rate per 100,000 Population for Both Sexes Related to Several Diseases for Limerick County in Comparison to All Other Counties and Regions

Cause of Death	2012	2013	2014	2015	2016	2017
(Acute myocardial infarction)						
All counties and regions	49.2	45.7	39.7	41.8	39.0	36.4
Limerick	67.3	66.3	52.0	56.0	62.4	54.1
All other malignant neoplasms						
All counties and regions	25.1	24.7	24.4	25.1	26.3	24.2
Limerick	30.8	29.8	31.2	23.9	27.8	25.0
Cancer of the trachea, bronchus and lung						
All counties and regions	39.2	39.7	41.6	39.0	40.3	40.2
Limerick	33.9	39.7	44.2	38.9	46.4	53.1
Cerebrovascular disease						
All counties and regions	42.1	42.5	39.9	41.0	38.6	35.7
Limerick	50.6	59.0	55.2	54.4	49.5	36.8
Chronic lower respiratory disease						
All counties and regions	34.6	35.9	33.4	36.3	36.1	33.6
Limerick	39.6	42.3	33.3	46.1	44.8	33.2
Complications of pregnancy, childbirth and puerperium						
All counties and regions	0.0	0.1	0.0	0.0	0.1	0.0
Limerick	0.0	0.5	0.0	0.0	0.0	0.0
Diseases of the blood and blood-forming organs, immunulogical disorders						
All counties and regions	2.1	2.2	2.0	1.9	1.9	2.0
Limerick	2.6	1.6	1.6	2.1	1.0	4.1
Diseases of the circulatory system						
All counties and regions	206.4	205.3	190.6	199.9	194.9	186.3
Limerick	248.3	246.3	232.6	237.5	231.4	189.5
Diseases of the digestive system						
All counties and regions	25.2	23.2	22.4	20.6	22.3	22.1
Limerick	29.2	24.0	25.5	23.3	23.7	13.3
Diseases of the nervous system and the sense organs						
All counties and regions	29.5	29.9	30.6	33.2	33.9	32.2
Limerick	40.7	28.2	34.3	33.2	41.2	37.3
Diseases of the respiratory system						
All counties and regions	76.1	75.9	75.2	82.5	83.0	85.1
Limerick	86.1	86.6	94.7	116.1	113.4	101.6

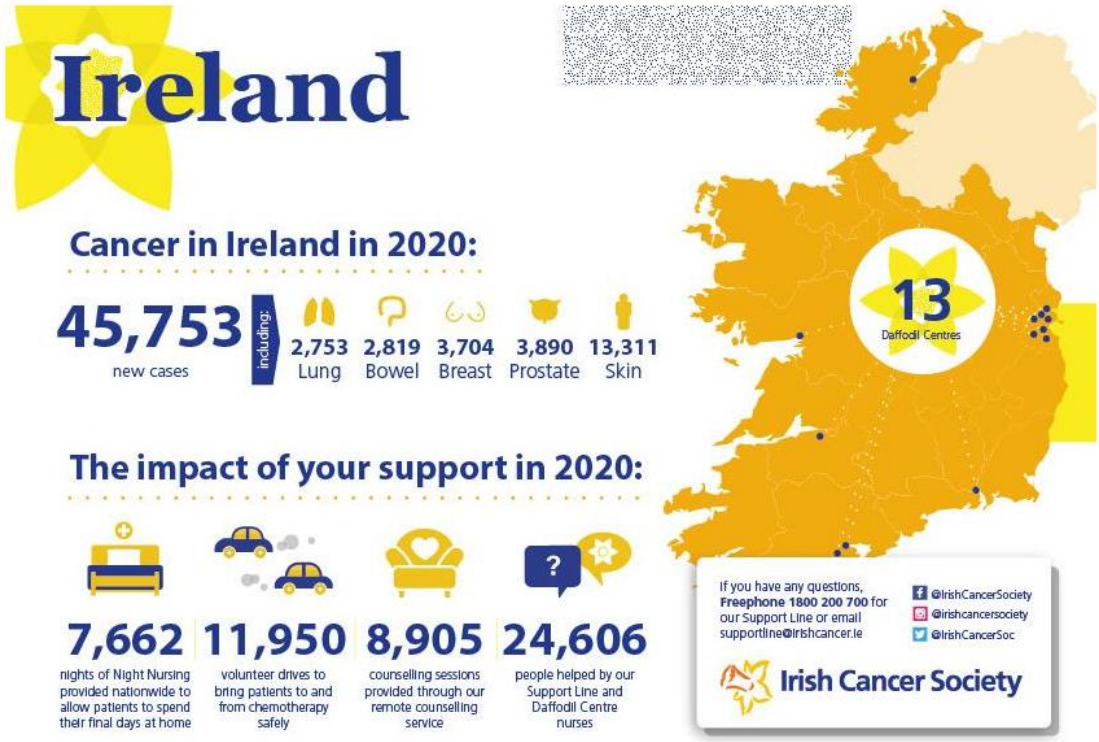
Cause of Death	2012	2013	2014	2015	2016	2017
Ischaemic heart disease						
All counties and regions	103.6	100.6	92.2	95.8	93.9	88.4
Limerick	130.4	123.2	110.3	112.5	104.6	90.4
Malignant neoplasm of bladder						
All counties and regions	4.6	4.6	5.4	5.1	4.3	4.4
Limerick	3.1	2.1	4.2	2.6	4.6	4.6
Malignant neoplasm of breast						
All counties and regions	15.2	15.5	15.9	14.5	16.1	15.8
Limerick	23.5	9.9	20.3	14.5	17.0	16.3
Malignant neoplasm of cervix uteri						
All counties and regions	2.0	1.7	2.1	1.9	1.6	1.7
Limerick	2.1	3.7	3.6	1.0	1.0	1.5
Malignant neoplasm of colon						
All counties and regions	11.8	11.3	10.7	10.3	10.6	9.8
Limerick	15.7	16.2	9.4	11.9	16.0	7.2
Malignant neoplasm of kidney						
All counties and regions	4.0	5.6	4.8	4.8	4.9	4.1
Limerick	5.2	7.8	7.3	3.6	3.1	3.6
Malignant Neoplasm of Larynx						
All counties and regions	1.6	1.2	1.5	1.2	1.4	1.5
Limerick	2.1	2.6	3.6	1.0	0.5	1.5
Malignant neoplasm of larynx and trachea/bronchus/lung						
All counties and regions	40.8	40.9	43.2	40.2	41.7	41.7
Limerick	36.0	42.3	47.9	39.9	46.9	54.6
Malignant neoplasm of lip, oral cavity, pharynx						
All counties and regions	3.7	3.5	3.6	4.0	4.0	4.1
Limerick	6.3	2.6	3.6	5.2	6.7	3.6
Malignant neoplasm of liver and the intrahepatic bile ducts						
All counties and regions	5.1	6.6	7.0	6.3	6.9	8.0
Limerick	3.1	7.8	8.8	11.4	12.4	11.7
Malignant neoplasm of lymph/haematopoietic tissue						
All counties and regions	16.7	15.7	15.6	15.6	15.4	16.2
Limerick	19.3	12.0	17.2	18.2	15.5	18.4

Cause of Death	2012	2013	2014	2015	2016	2017
Malignant neoplasm of oesphagus						
All counties and regions	8.2	8.1	8.3	8.7	9.1	8.2
Limerick	9.4	6.3	8.8	7.8	10.8	8.2
Malignant neoplasm of other parts of the uterus						
All counties and regions	2.3	2.4	2.8	3.1	2.9	2.6
Limerick	2.1	2.6	2.6	1.0	1.6	4.1
Malignant neoplasm of ovary						
All counties and regions	6.0	5.7	6.0	5.7	6.2	6.4
Limerick	4.7	6.8	10.4	5.2	6.2	9.2
Malignant neoplasm of pancreas						
All counties and regions	10.4	10.7	11.1	11.7	10.9	11.0
Limerick	11.5	8.4	12.5	12.4	11.9	12.8
Malignant neoplasm of prostate						
All counties and regions	11.3	10.8	11.6	11.2	10.7	12.2
Limerick	10.4	13.1	8.8	11.9	11.9	9.7
Malignant neoplasm of rectum and anus						
All counties and regions	9.6	11.0	10.5	11.3	11.3	11.6
Limerick	13.0	11.0	8.3	11.4	9.3	13.3
Malignant neoplasm of skin						
All counties and regions	3.1	3.9	3.4	2.9	3.7	3.1
Limerick	3.1	3.1	5.2	1.6	2.6	1.5
Malignant neoplasm of stomach						
All counties and regions	6.8	6.5	7.9	7.0	6.9	6.6
Limerick	5.7	7.3	7.8	8.3	4.6	4.1
Malignant neoplasms						
All counties and regions	186.6	189.1	194.2	189.4	193.5	191.5
Limerick	205.0	192.6	218.0	191.8	209.8	209.4
Other diseases of the circulatory system						
All counties and regions	30.4	29.0	27.3	29.3	28.1	27.7
Limerick	30.8	27.1	34.3	34.2	32.5	23.0
Other diseases of the respiratory system						
All counties and regions	17.8	18.4	19.6	20.6	23.3	27.2
Limerick	18.3	17.2	29.7	23.9	32.5	33.2

4. **Cancer Incidence in Ireland** [Reference: Cancer statistics | Irish Cancer Society https://www.bing.com/search?q=national+cancer+registry+ireland&src=IE-SearchBox&FORM=IESR4A]

Since its inception in October 1963, the Irish Cancer Society foster and promotes research devoted to the study of the origin and advance the relief, cure, treatment and prevention of cancer or any diseases of similar nature. The Irish Cancer Society collects cancer health data on a national level and as such, the following summarizes the cancer incidence rate most prevalent in Ireland:

Figure 4.5 Cancer in Ireland in 2020



According to the Irish Cancer Society, 1 in 4 deaths in Ireland is caused by cancer with 30% of total deaths attributable to cancer every year. Further, smoking increases cancer risks, causing one third of all cancers and 9 of 10 lung cancers caused by smoking.

The Irish Cancer Society does not provide Limerick-specific cancer data.

4.3 EXPOSURE PATHWAYS OF CONCERN

A complete exposure pathway requires the following four elements:

- The presence of a chemical substance;
- A migration pathway (environmental transport);
- An exposure point for contact (e.g., air); and
- An exposure route (e.g., inhalation).

An exposure pathway is not complete unless all four elements are present. If a pathway is incomplete, no significant exposure is anticipated to occur.

As described below, two exposure pathways of concern were identified at the problem formulation stage for human receptors: 1) inhalation of COPCs in ambient air, and 2) direct contact with COPCs as particulates emitted from the AAL plant via atmospheric deposition.

4.3.1 INHALATION OF AMBIENT AIR

The HHA evaluated potential health effects associated with acute (short-term) and chronic (long-term) inhalation exposures to ambient concentrations of identified COPCs that may be influenced by emissions from the Project. These emissions are released into ambient air primarily as particulates and may be subsequently inhaled by human receptors within the Project Study Area.

Details of the exposure assessment are provided in **Section 5**.

4.3.2 ATMOSPHERIC DEPOSITION

The Air Quality Impact Assessment (AWN, 2021) evaluated dust deposition levels across thirty-five (35) monitoring stations located within the facility boundary from January 2016 to December 2020. The rate of deposition from the air quality modelling can be used to estimate changes in future soil concentrations within the Study Area.

The concern from a health perspective is focussed on particles of dust which are less than or equal to 10 microns (PM_{10}) and less than or equal to 2.5 microns ($PM_{2.5}$). With respect to larger dust particles that can give rise to nuisance dust, there are no statutory guidelines regarding the maximum dust deposition levels that may be generated during the construction phase of a development in Ireland. Regarding dust deposition, the German TA-Luft standard for dust deposition (non-hazardous dust) sets a maximum permissible emission level for dust deposition of 350 mg/m^2-day averaged over a 30-day period at any receptors outside the Site boundary.

The predicted annual concentration (excluding background) at the worst-case location peaks at 13.1 mg/m^2/day. Based on a background dust deposition level of 20 mg/m^2/day in the region, the annual dust deposition level due to emissions from the BRDA and associated construction works is at 33.1 mg/m^2/day. This peak level is well below the German TA-Luft standard for dust deposition, comprising only 9.5% of the annual guideline.

Additionally, the predicted Project rate of deposition was further compared to two Canadian dustfall objectives. The predicted rate of deposition was converted to 0.331 mg/dm^2/day and then compared against the British Columbia Ministry of Environment and Climate Change Strategy (BC MoECCS) dustfall objective of 2.90 mg/dm^2/day for industrial land use and was found to be less than 1% of the standard. It is noted that in 2020, B.C. MoECCS released guidance indicating that the dustfall Pollution Control Objectives are no longer relied upon, except in limited circumstances, such as *concerns of an aesthetic or nuisance nature*. Given that the worst-case predicted rate of deposition of particulate matter is expected to be several orders of magnitude lower than the standard, it is considered that this provides sufficient evidence that there would be no measurable change in soil quality from depositional contributions via dustfall from the BRDA.

Furthermore, the Ontario Ministry of the Environment, Conservation and Parks (MECP) human toxicology and air standards section of their Standards and Development Branch developed a 30-day and annual Ambient Air Quality Criterion (AAQC) for dustfall based on effects on aesthetics from the deposition of the contaminant (i.e., soiling). The worst-case predicted deposition rate of 33.1 mg/m^2/day was converted to 0.0331 g/m^2/day resulting in a calculated cumulative deposition rate of 0.993 g/m^2 assuming daily deposition for a 30-day period. This 30-day value is only 14% of the 30-day Ontario AAQC of 7 g/m^2.

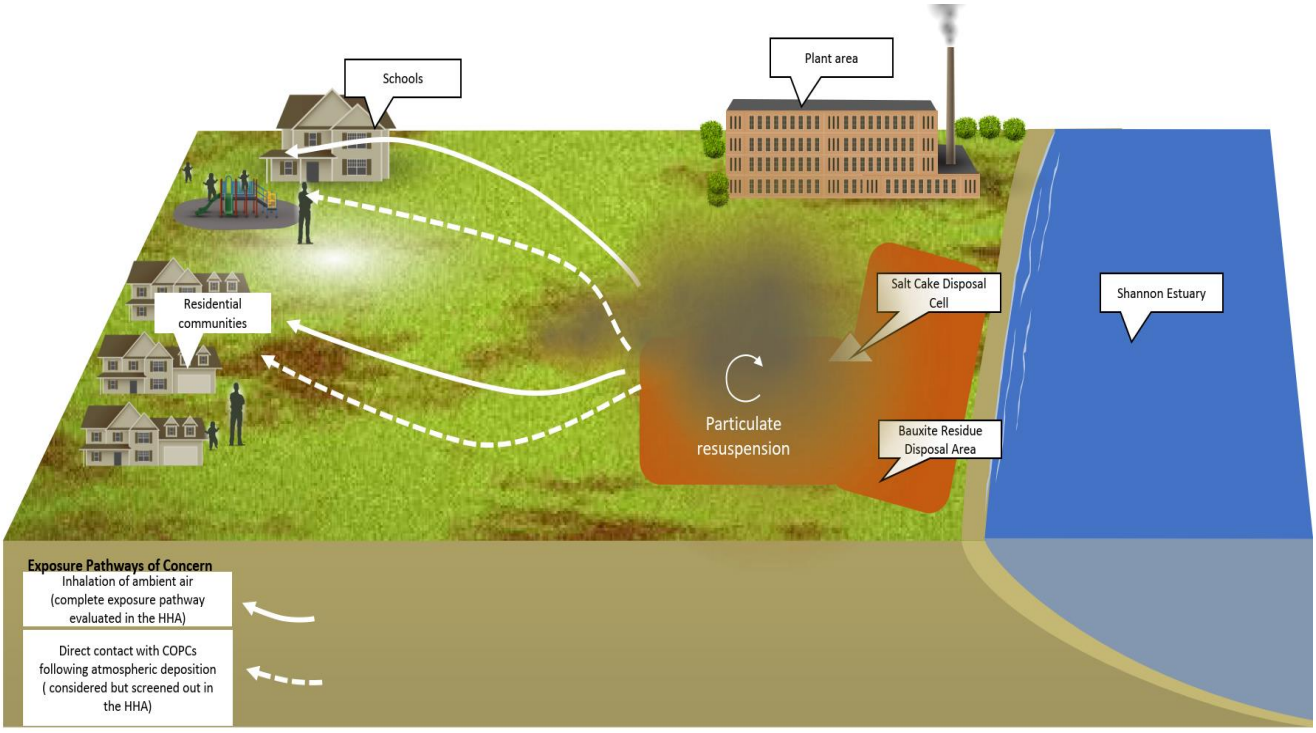
Given that in all cases, the worst-case predicted rate of deposition is shown to be significantly less than the above-noted standards, it is considered that atmospheric dust deposition would have a *de minimis* impact on the quality of soil and/or food items grown within the Study Area. No further evaluation of deposition is therefore warranted; the inhalation exposure pathway is the only pathway carried forward for quantitative assessment in the HHA.

4.4 CONCEPTUAL SITE EXPOSURE MODEL

A Conceptual Site Exposure Model (CSM) is developed in a health risk assessment to understand which COPCs are present in the study area, how receptors may use the area, and the pathways of contact that are possible between the identified COPCs and the receptors. These substances, receptors, and pathways (the environmental risk components) are examined in detail to identify the "reasonably anticipated" combinations corresponding to potentially complete exposure pathways. Unreasonable or incomplete pathways are eliminated from further consideration or are "screened out". The combinations of the environmental components that remain subsequent to the screening process, form the basis of the conceptual model, and are used to focus the health risk assessment.

The CSM for the Project is shown on **Figure 4.6**. Given that this HHA focussed on particulate emissions from the Project and their potential effect on nearby human receptors, the only complete exposure pathway assessed was inhalation of Project-specific emissions of COPCs.

Figure 4.6 Conceptual Site Exposure Model for the HHA



4.5 UNCERTAINTY ANALYSIS

A summary of the major assumptions made in the Problem Formulation stage of the HHA and resulting uncertainties is provided below:

- Information related to the environmental fate and transport, toxicology and health effects associated with bauxite residues are lacking or limited. The findings of the literature review indicate that bauxite residue is inert, non-corrosive, non-irritant and non-hazardous. Given that bauxite residue is a mixture, the HHA was carried out by evaluating its constituents and their associated toxicology and health effects. As such, evaluating the constituents of bauxite residue maintains a conservative approach.
- Information related to the environmental fate and transport, toxicology and health effects associated with salt cake are lacking or limited. The findings of the literature review indicate that salt cake is an irritant and hazardous. Given that bauxite residue is a mixture, the HHA was carried out by evaluating its constituents and their associated toxicology and health effects. As such, evaluating the constituents of salt cake maintains a conservative approach.
- For the purposes of exposure modelling, it has been assumed that the predicted concentrations of COPCs in outdoor air are equal to that in indoor air (i.e., established equilibrium). Ambient indoor air concentrations are dependant on a multitude of variables including infiltration rates, indoor decay rates, ventilation system set-ups, and other factors. To maintain a conservative approach, the assumption that equilibrium is established between outdoor and indoor ambient air was applied for this assessment.
- It was considered that all human receptors may be exposed to maximum impacts associated with ambient concentrations of identified COPCs that may be influenced by emissions from the Project. This approach is overly conservative; the probability of human presence should be accounted for in the risk characterization.

5 EXPOSURE ASSESSMENT

The Exposure Assessment step was conducted for each COPC-pathway-receptor combination identified in the Problem Formulation to estimate the amount of COPCs that human receptors are potentially exposed to. For the purposes of the exposure modelling, it was assumed that the predicted concentration of COPCs in outdoor ambient air was equal to that in indoor air (i.e., established equilibrium). Exposure estimates were calculated from estimated near ground level maximum concentrations of each identified COPC and receptor-specific parameters such as exposure frequency and duration. Conservative assumptions were applied in this step of the HHA to ensure that it is protective of health including sensitive subpopulations (e.g., children, elderly, asthmatics).

5.1 PREDICTED CONCENTRATIONS OF COPCS IN AMBIENT AIR

The assessment of COPC exposure concentrations relies on the air dispersion modelling to support the assessment of sensitive human receptors evaluated in this HHA. To assess the impact of the proposed development at sensitive receptors beyond the AAL facility boundary, and at specific sensitive locations, air dispersion modelling was undertaken. Modelling using the US EPA new generation dispersion model AERMOD (version 21112) was used. The US EPA have recommended this model for assessing air quality emissions from industrial facilities. The model is a steady-state Gaussian plume model used to assess pollutant concentrations associated with industrial sources including dust emissions from area sources. The model has been designated the regulatory model by the US EPA for modelling emissions from industrial sources in both flat and rolling terrain. The AERMET meteorological pre-processor was used to generate hourly boundary layer parameters for use by AERMOD. The air dispersion modelling input data consists of detailed information on the physical environment (including land use and terrain features), emission rate information and a full year of meteorological data. Using this input data, the air dispersion model predicts ambient ground level concentrations for each hour of the modelled meteorological year. The model post-processes the data to identify the location and maximum value of the worst-case ground level concentration in the applicable format for comparison with the relevant limit values. The worst-case concentration is then added to the existing baseline concentration, where relevant, to give the worst-case predicted ambient concentration level of the relevant pollutants. Full details of the model inputs are included in *Chapter 11 – Air Quality* provided in the EIAR.

5.1.1 OPERATIONAL PHASE SITE ACTIVITY

During the operation phase of the BRDA, the existing activities will continue; however, the phasing of the BRDA raise over time will result in a higher elevation above ground level where these activities will take place. The salt cake cell will also be raised as part of the proposed BRDA raise. However, the salt cake, due to the high moisture content of approximately 45%, will not be a significant source of dust. For the purposes of this assessment, the following stages of the BRDA development have been assessed:

- Current (Scenario 1);
- Phase 1 at Stage 10; Phase 2 at Stage 4 (Scenario 2);
- Phase 1 at Stage 12; Phase 2 at Stage 8 (Scenario 3);
- Phase 1 at Stage 14; Phase 2 at Stage 12 (Scenario 4); and
- All at Stage 16 with restoration (Scenario 5).

There will be no increase in light vehicle trips, however there will be a small increase in heavy vehicle trips projected on the external road network, specifically associated with the importation of soil and soil improver associated with the proposed raising of the BRDA. The closest residential dwellings to the Project are located at a distance greater than 900 m from the boundary.

In relation to the BRDA and Borrow Pit, the construction and operational phases are considered together in the air dispersion modelling assessment given that the operation of the BRDA will also involve the construction of each stage elevation which in turn will require the extraction of material from the Borrow Pit. Thus, $PM_{2.5}$ emissions from the BRDA were assumed to coincide with an emission of dust from the Borrow Pit in all modelling scenarios outlined in the assessment.

During both the operational and construction phase, which are considered together, the potential sources of $PM_{2.5}$ are those associated with the raising of the BRDA, the Borrow Pit extraction and internal site vehicle movements to the BRDA area where the phasing will see the height of the existing BRDA increase from Stage 10 to Stage 16.

Activity within the Borrow Pit will include occasional blasting to remove rock, on site breaking and crushing of the rock and excavator and dump truck movements to stockpile the materials. On the BRDA, there will be a range of excavators and other equipment for residue farming. The nearest sensitive location is greater than 500 m from the BRDA.

5.1.2 PM_{10} MODELLING RESULTS AT SENSITIVE RECEPTORS

Predicted PM_{10} concentrations at the AAL boundary are below the ambient air quality standards at the worst-case off-site location due to emissions from the BRDA plus the borrow pit and its associated traffic moments. Modelling for each of the five scenarios was investigated (see **Table 5.1**) and discussed in *Chapter 11 – Air Quality* provided in the EIAR.

The predicted 24-hour (90^{th}%ile) and annual concentrations (excluding background) at the worst-case off-site location peak at 4.7 and 1.4 $\mu g/m^3$, respectively with peaks generally located at the site boundary. Based on a background PM_{10} concentration of 10 $\mu g/m^3$ in the region, the combined annual PM_{10} concentration including the emissions form the BRDA and borrow pit peaks at 11.4 $\mu g/m^3$.

This predicted level equates to at most 28.5% of the annual limit value of 40 $\mu g/m^3$. The predicted 24-hour PM_{10} concentration (including background) peaks at 14.7 $\mu g/m^3$ which is 29.4% of the 24-hour limit value of 50 $\mu g/m^3$ (measured as a 90.4^{th}%ile). Concentrations at the worst-case sensitive receptor are significantly lower than the worst-case off-site location.

Results are broadly similar for Scenarios 1 through 4 with a tendency to slightly decrease in ambient concentration as the BRDA is raised. Scenario 5 (all at stage 16 but still unvegetated) is lower as the surface area of the BRDA is significantly reduced compared to the other four scenarios.

Table 5.1 **Air Dispersion Modeling Results for PM_{10} for Scenarios 1 through 5 – Worst-Case Sensitive Receptor**

POLLUTANT / SCENARIO	AVERAGING PERIOD	OPERATIONAL CONTRIBUTION ($\mu g/m^3$)	ANNUAL MEAN BACKGROUND ($\mu g/m^3$) NOTE 1	PREDICTED ENVIRONMENTAL CONCENTRATION (PEC) PM_{10} ($\mu g/m^3$)	EU LIMIT VALUE ($\mu g/m^3$)	PEC AS A PERCENTAGE OF LIMIT VALUE
PM_{10} / Scenario 1	Annual mean	1.4	10	11.4	40	28.5%
	90.4th%ile of 24-hr Means	4.7	10	14.7	50	29.4%
PM_{10} / Scenario 2	Annual mean	1.4	10	11.4	40	28.5%
	90.4th%ile of 24-hr Means	4.7	10	14.7	50	29.4%
PM_{10} / Scenario 3	Annual mean	1.3	10	11.3	40	28.3%
	90.4th%ile of 24-hr Means	4.7	10	14.7	50	29.4%
PM_{10} / Scenario 4	Annual mean	1.3	10	11.3	40	28.3%
	90.4th%ile of 24-hr Means	4.6	10	14.6	50	29.2%
PM_{10} / Scenario 5	Annual mean	0.50	10	10.5	40	26.3%
	90.4th%ile of 24-hr Means	1.3	10	11.3	50	22.6%

Note 1 S.I. 180 of 2011 and EU Directive 2008/50/EC

5.1.3 $PM_{2.5}$ MODELLING RESULTS AT SENSITIVE RECEPTORS

Predicted $PM_{2.5}$ concentrations due to emissions from the BRDA plus the borrow pit and its associated traffic moments are below the ambient air quality standard at the nearest sensitive receptors. Modelling for each of the five scenarios has been investigated (see **Table 5.2**). The predicted annual concentration (excluding background) at the worst-case sensitive receptor peaks at 0.45 $\mu g/m^3$. Based on a background $PM_{2.5}$ concentration of 7 $\mu g/m^3$ in the region, the combined annual $PM_{2.5}$ concentration including the emissions from the BRDA and borrow pit peaks at 7.45 $\mu g/m^3$. This predicted level equates to at most 29.8% of the annual limit value of 25 $\mu g/m^3$.

The predicted maximum 24-hour concentration (excluding background) at the worst-case sensitive receptor peaks at 13.2 $\mu g/m^3$. Based on a background $PM_{2.5}$ concentration of 7 $\mu g/m^3$ in the region, the combined annual $PM_{2.5}$ concentration including the emissions form the BRDA and borrow pit peaks at 20.2 $\mu g/m^3$.

Results are broadly similar for Scenarios 1 through 4 with a tendency to slightly decrease in ambient concentration as the BRDA is raised. Scenario 5 (all at stage 16) is lower as the surface area of the BRDA is significantly reduced compared to the other four scenarios.

Table 5.2 **Air Dispersion Modeling Results for PM2.5 for Scenarios 1 through 5 – Worst-Case Sensitive Receptor**

POLLUTANT / SCENARIO	AVERAGING PERIOD	BRDA & BORROW PIT CONTRIBUTION ($\mu g/m^3$)	ANNUAL MEAN BACKGROUND ($\mu g/m^3$)[1]	PREDICTED ENVIRONMENTAL CONCENTRATION (PEC) $PM_{2.5}$ ($\mu g/m^3$)	EU LIMIT VALUE ($\mu g/m^3$)	PEC AS PERCENTAGE OF LIMIT VALUE
$PM_{2.5}$ / Scenario 1	Annual mean	0.44	7	7.44	25	29.8%
	Maximum 24-hr Mean	12.7	7	19.7	N/A	N/A
$PM_{2.5}$ / Scenario 2	Annual mean	0.45	7	7.45	25	29.8%
	Maximum 24-hr Mean	13.2	7	20.2	N/A	N/A
$PM_{2.5}$ / Scenario 3	Annual mean	0.43	7	7.43	25	29.7%
	Maximum 24-hr Mean	12.4	7	19.4	N/A	N/A
$PM_{2.5}$ / Scenario 4	Annual mean	0.42	7	7.42	25	29.7%
	Maximum 24-hr Mean	11.9	7	18.9	N/A	N/A
$PM_{2.5}$ / Scenario 5	Annual mean	0.13	7	7.13	25	28.5%
	Maximum 24-hr Mean	5.2	7	12.2	N/A	N/A

5.1.4 $PM_{2.5}$ MODELLING RESULTS AT SCOIL NAISIUNTA SHEANAIN

Predicted $PM_{2.5}$ concentrations due to emissions from the BRDA plus the borrow pit and its associated traffic moments are below the ambient air quality standard at Scoil Naisiunta Sheanain. Modelling for each of the five scenarios has been investigated (see **Table 5.3**). The predicted annual concentration (excluding background) at Scoil Naisiunta Sheanain peaks at 0.0026 $\mu g/m^3$. Based on a background $PM_{2.5}$ concentration of 7 $\mu g/m^3$ in the region, the combined annual $PM_{2.5}$ concentration including the emissions form the BRDA and borrow pit peaks at 7.0026 $\mu g/m^3$. This predicted level equates to at most 28.0% of the annual limit value of 25 $\mu g/m^3$.

The predicted maximum 24-hour concentration (excluding background) at Scoil Naisiunta Sheanain peaks at 0.14 $\mu g/m^3$. Based on a background $PM_{2.5}$ concentration of 7 $\mu g/m^3$ in the region, the combined annual $PM_{2.5}$ concentration including the emissions form the BRDA and borrow pit peaks at 7.14 $\mu g/m^3$.

Results are broadly similar for Scenarios 1 – 4 with a tendency to slightly decrease in ambient concentration as the BRDA is raised. Scenario 5 (all at stage 16) is lower as the surface area of the BRDA is significantly reduced compared to the other four scenarios.

Table 5.3 Air Dispersion Modeling Results for $PM_{2.5}$ for Scenarios 1 through 5 – Scoil Naisiunta Sheanain

POLLUTANT / SCENARIO	AVERAGING PERIOD	BRDA & BORROW PIT CONTRIBUTION ($\mu g/m^3$)	ANNUAL MEAN BACKGROUND ($\mu g/m^3$) NOTE 1	PREDICTED ENVIRONMENTAL CONCENTRATION (PEC) $PM_{2.5}$ ($\mu g/m^3$)	EU LIMIT VALUE ($\mu g/m^3$)	PEC AS A PERCENTAGE OF LIMIT VALUE
$PM_{2.5}$ / Scenario 1	Annual mean	0.0026	7	7.0026	25	28.0%
	Maximum 24-hr Mean	0.14	7	7.14	N/A	N/A
$PM_{2.5}$ / Scenario 2	Annual mean	0.0026	7	7.0026	25	28.0%
	Maximum 24-hr Mean	0.14	7	7.14	N/A	N/A
$PM_{2.5}$ / Scenario 3	Annual mean	0.0026	7	7.0026	25	28.0%
	Maximum 24-hr Mean	0.14	7	7.14	N/A	N/A
$PM_{2.5}$ / Scenario 4	Annual mean	0.0026	7	7.0026	25	28.0%
	Maximum 24-hr Mean	0.14	7	7.14	N/A	N/A
$PM_{2.5}$ / Scenario 5	Annual mean	0.0019	7	7.0019	25	28.0%
	Maximum 24-hr Mean	0.086	7	7.086	N/A	N/A

5.1.5 PREDICTED CONCENTRATIONS OF COPCS IN AMBIENT AIR

The HHA assumed that emissions of the bauxite residue and salt cake predominantly occurs as particulates or fugitive dusts. To assess potential exposures to bauxite residue and salt cake, this HHA assumed their constituents will be present in the dusts emitted from the Project at the same percentage composition. That is, the predicted concentration for each COPC is based on the percentage of each COPC modelled PM_{10} (annual and 24-hr) and $PM_{2.5}$ (annual and 24-hr) concentrations to reflect the percentage of each COPC in the dust. Therefore, this HHA assumes that both bauxite residue and salt cake are both present as dust, with levels of their constituents present at the same percentage composition as in the solid waste by-product. This assumption maintains an overly conservative approach given that the moisture content of both bauxite residue (21%) and salt cake (41% to 46%, with a mean of 44%) are high. The presence of salt cake constituents as particulates or dust is highly unlikely given its moisture content.

It should be noted that whilst modelling for all five (5) scenarios was investigated as part of the Air Quality Impact Assessment, only the predicted concentrations from the worst-case scenarios [i.e., scenario 1 for PM_{10} (annual and 24-hr) and scenario 2 for $PM_{2.5}$ (annual and 24-hr)] were considered for the purpose of the exposure assessment. For both PM_{10} and $PM_{2.5}$, air dispersion modelling results for scenarios 1 through 5 generally showed a slight decrease in predicted ambient concentrations as the BRDA is raised (i.e., with each successive scenario), with the highest modelled concentrations being those from scenarios 1 and 2.

Table 5.4 Exposure Concentrations of Bauxite Residue and Salt Cake Constituents

BAUXITE RESIDUE CONSTITUENTS (COPCS)	EXPOSURE CONCENTRATION BASED ON PM_{10} ANNUAL (mg/m^3)[1]	EXPOSURE CONCENTRATION BASED ON PM_{10} 24-HR (mg/m^3)[2]	EXPOSURE CONCENTRATION BASED ON $PM_{2.5}$ ANNUAL (mg/m^3)[3]	EXPOSURE CONCENTRATION BASED ON $PM_{2.5}$ 24-HR (mg/m^3)[4]	W/W%[5]
Aluminium Geothite	2.9E-04	9.8E-04	9.4E-05	2.8E-03	20.9
Hematite	2.6E-04	8.8E-04	8.4E-05	2.5E-03	18.75
Anatase and Rutile	5.7E-05	1.9E-04	1.8E-05	5.4E-04	4.1
Boehmite	3.0E-05	1.0E-04	9.7E-06	2.8E-04	2.15
Zircon	4.2E-06	1.4E-05	1.4E-06	4.0E-05	0.3
Gypsum	2.1E-06	7.1E-06	6.8E-07	2.0E-05	0.15
Sodium Sulphate	1.1E-06	3.5E-06	3.4E-07	9.9E-06	0.075
Sodium Fluoride	2.8E-07	9.4E-07	9.0E-08	2.6E-06	0.02
Chromium Trioxide	2.8E-06	9.4E-06	9.0E-07	2.6E-05	0.2
Vanadium Pentoxide	2.8E-06	9.4E-06	9.0E-07	2.6E-05	0.2
Manganese Oxide	4.9E-07	1.6E-06	1.6E-07	4.6E-06	0.12
Arsenic Trioxide	1.4E-07	4.7E-07	4.5E-08	1.3E-06	0.01
Zinc Oxide	7.0E-08	2.4E-07	2.3E-08	6.6E-07	0.005
Lead Oxide	9.8E-08	3.3E-07	3.2E-08	9.2E-07	0.007
Yttrium Trioxide	1.3E-07	4.5E-07	4.3E-08	1.3E-06	0.0095
Copper Oxide	5.6E-08	1.9E-07	1.8E-08	5.3E-07	0.004
Strontium Oxide	1.3E-07	4.5E-07	4.3E-08	1.3E-06	0.0095
Cerium Oxide	2.8E-07	9.4E-07	9.0E-08	2.6E-06	0.02
Calcium Cancirnite	1.7E-04	5.7E-04	5.5E-05	1.6E-03	12.15
Gallium Trioxide	1.2E-07	4.0E-07	3.8E-08	1.1E-06	0.0085
Hydrogarnet	4.1E-05	1.4E-04	1.3E-05	3.9E-04	2.95
Perovskite	5.7E-05	1.9E-04	1.9E-05	5.4E-04	4.1
Niobium Pentoxide	2.0E-07	6.6E-07	6.3E-08	1.9E-06	0.014
Thorium Oxide	1.4E-07	4.7E-07	4.5E-08	1.3E-06	0.01
SALT CAKE CONSTITUENTS (COPCS)					
Sodium Oxalate	2.2E-04	7.5E-04	1.3E-03	2.1E-03	16
Aluminium Oxide	1.4E-04	4.7E-04	8.4E-04	1.3E-03	10

Notes:

[1] Worst-case (scenario 1) annual mean concentration of PM_{10} (Project contribution) is equal to 1.4 $\mu g/m^3$

[2] Worst-case (scenario 1) 24-hr 90.4 percentile mean concentration of PM_{10} (Project contribution) is equal to 4.7 $\mu g/m^3$

[3] Worst-case (scenario 2) annual mean concentration of $PM_{2.5}$ (Project contribution) is equal to 0.45 $\mu g/m^3$

[4] Worst-case (scenario 2) 24-hr mean concentration of $PM_{2.5}$ (Project contribution) is equal to 13.2 $\mu g/m^3$

[5] Percent (%) weight of constituent COPC per total Bauxite Residue or Salt Cake weight

5.2 EXPOSURE PARAMETERS FOR WORKERS

In this exposure scenario, a worker is considered an adult teacher (i.e., >20 years) who is employed on a full-time basis and spends 9 hours/day, 5 days/week, 48 weeks/year (assuming a four-week vacation period) at the Scoil Naisiunta Sheanain primary school. A typical day involves a nine-hour work shift, five days per week, for 48 weeks of the year (i.e., assuming 4 weeks of vacation per year). The exposure parameters applicable to adult workers in a workplace setting near the Project are as follows:

Table 5.5 Exposure Parameters for Adult Workers

EXPOSURE FACTOR	UNITS	ADULT (≥ 20 YRS)	REFERENCE
EF (exposure frequency for inhalation) = EFa x EFb x EFc	h/yr	2160	Calculated
EFa (daily exposure frequency)	d/wk	5	US EPA, 2011
EFb (weekly exposure frequency)	wk/yr	48	OWTA, 1997
EFc (hourly exposure frequency)	h/d	9	US EPA, 2011
ED (exposure duration)	yr	58	US EPA, 2011
AP (averaging period): non-cancer	yr	58	US EPA, 2011
AP (averaging period): cancer	yr	78	US EPA, 2011

Notes:
h – hour; yr – year; wk – week; d – day.

5.3 EXPOSURE PARAMETERS FOR CHILDREN AND TEENS IN SCHOOL

As discussed in **Section 4.2**, Scoil Naisiunta Sheanain, a primary school with approximately 90 students, is located 1.9 km to the west of the BRDA. Children, aged 5 to 13 years old, are attending the school for a typical nine-hour day (including before and after school programs), five days per week, for 38 weeks/year (i.e., typical length of school year). The exposure parameters applicable to children and teen-aged students are as follows:

Table 5.6 Exposure Parameters for School-Aged Children and Teens

EXPOSURE FACTOR	UNITS	CHILD (5 – 11 YRS)	TEEN (12 -13 YRS)	REFERENCE
EF (exposure frequency for inhalation) = EFa x EFb x EFc	h/yr	1710	1710	Calculated
EFa (daily exposure frequency)	d/wk	5	5	US EPA, 2011
EFb (weekly exposure frequency)	wk/yr	38	38	Site-specific
EFc (hourly exposure frequency)	h/d	9	9	US EPA, 2011
ED (exposure duration)	yr	7	2	US EPA, 2011
AP (averaging period): non-cancer	yr	7	2	US EPA, 2011
AP (averaging period): cancer	yr	78	78	US EPA, 2011

Notes:
h – hour; yr – year; wk – week; d – day.

5.4 EXPOSURE PARAMETERS FOR RESIDENTS

In this exposure scenario, a resident receptor represents various life stages including infant, toddler, child, teenager, and adults. Residents were considered to spend 24 hours/day, 7 days/week, 48 weeks/year (assuming a four-week vacation). The exposure parameters applicable to residents are as follows:

Table 5.7 Exposure Parameters for Residents

EXPOSURE FACTOR	UNITS	INFANT (0 – 6 MO.)	TODDLER (7 MO. TO 4 YRS)	CHILD (5 – 11 YRS)	TEEN (12 – 19 YRS)	ADULT (≥ 20 YRS)	REFERENCE
EF (exposure frequency for inhalation) = EFa x EFb x EFc	h/yr	806	8064	8064	8064	8064	Calculated
EFa (daily exposure frequency)	d/wk	7	7	7	7	7	US EPA, 2011
EFb (weekly exposure frequency)	wk/yr	48	48	48	48	48	OWTA, 1997
EFc (hourly exposure frequency)	h/d	24	24	24	24	24	US EPA, 2011
ED (exposure duration)	yr	0.5	4.5	7	8	58	US EPA, 2011
AP (averaging period): non-cancer	yr	0.5	4.5	7	8	58	US EPA, 2011
AP (averaging period): cancer	yr	78	78	78	78	78	US EPA, 2011

Notes:
h – hour; yr – year; wk – week; d – day; mo – months.

5.5 UNCERTAINTY ANALYSIS

A summary of the major assumptions made in the Exposure Assessment stage of the HHA and resulting uncertainties are provided below:

- Conservative assumptions were applied when calculating the exposure estimates (i.e., conservative assumptions for exposure durations and frequencies). For example, residents were assumed to be exposed to predicted exposure concentrations at the Project boundary continuously, for 24-hours, daily.
- The exposure assessment only considered predicted air concentrations from scenario 1, which represents the earliest stage of BRDA elevation construction and the worst-case predicted air concentrations. Predicted air concentrations show a slight decrease as the BRDA is raised (i.e., with each successive scenario), with the final scenario (5) having the lowest predicted air concentrations as the surface area of the BRDA is significantly reduced compared to the other scenarios. Therefore, using predicted air concentrations from scenario 1 for the purpose of the exposure assessment is considered a conservative approach, and is likely to overestimate risk.
- The air dispersion model used to calculate predicted PM_{10} and $PM_{2.5}$ ambient ground level concentrations generated by the AAL facility only (i.e., operational contribution) also identified the concentrations at the worst-case off-site locations. These worst-case concentrations were selected to develop the COPC-specific exposure concentrations used for the purpose of the exposure assessment. Given that these concentrations are based along the AAL facility boundary, and that the nearest off-site receptor is located approximately 1.9 kilometres to the west of the AAL facility, use of these worst-case concentrations is considered a conservative approach, and is likely to overestimate risk.
- The HHA assumed that emissions of the bauxite residue and salt cake predominantly occurs as particulates or fugitive dusts. To assess potential exposures to bauxite residue and salt cake, this HHA assumed their constituents will be present in the dusts emitted from the Project at the same percentage composition. That is, the predicted concentration for each COPC is based on the percentage of each COPC modelled PM_{10} (annual and 24-hr) and $PM_{2.5}$ (annual and 24-hr) concentrations to reflect the percentage of each COPC in the dust. Therefore, this HHA assumes that both bauxite residue and salt cake are both present as dust (i.e., exposures to PM have been doubled), with levels of their constituents present at the same percentage composition as in the

solid waste by-product. This assumption maintains an overly conservative approach given that the moisture content of both bauxite residue (21%) and salt cake (41% to 46%, with a mean of 44%) are high. The presence of salt cake constituents as particulates or dust is highly unlikely given its moisture content.

- For the purposes of exposure modelling, it has been assumed that human receptors, whether in an indoor environment or outdoor environment, would be continuously exposed to ground-level COPC concentrations in ambient air throughout the duration of their time at the given receptor location. Ambient indoor air concentrations are dependant on a multitude of variables including building infiltration rates, indoor decay rates, ventilation system setups, and other factors. To maintain a conservative approach, the assumption that equilibrium is established between outdoor and indoor ambient air was applied for this assessment.

6 HAZARD ASSESSMENT

The hazard assessment step provides the basis for evaluating what is an acceptable exposure and what level of exposure may be harmful to human health. This step involves identification of potentially harmful effects associated with each COPC and determines the dose that a receptor can be exposed to without experiencing unacceptable effects. This value is called the toxicity reference value (TRV).

Exposure limits are typically selected from TRVs published by appropriate regulatory agencies or, in cases where regulatory values are not available, a literature review is conducted, and published toxicity studies are reviewed and evaluated to derive a TRV. In this HHA, exposure limits are used for the quantitative estimation of risks.

Exposure limits are derived based on the duration of exposure. For this HHA, exposure limits for each COPC were selected to evaluate long-term (chronic) exposures representing repeated exposures over longer term periods that are conservatively assumed to take place over a lifetime.

Short-term (acute) exposures represent single or intermittent exposures lasting up to 24-hours. The findings of the literature review are summarized in chemical-specific toxicity profiles and are provided in **Appendix E.** Information related to health effects and exposure limits associated with acute exposures for identified COPCs is limited or lacking. Acute effects reported in literature generally include irritation of the eyes and upper respiratory tract and are summarized in the chemical-specific toxicity profiles (see **Appendix E**), where available.

6.1 REVIEW OF TOXICOLOGY DATA FOR BAUXITE RESIDUE

The findings of the literature search identified three studies (Czovek 2011; Gelencser 2011; Gundy 2013) that characterize the potential health risks associated with the inhalation of red mud dusts. Following accidental collapse of the red-mud containing reservoir on October 4, 2010, a highly alkaline red mud sludge was discharged into agricultural and residential lands near Ajka in Hungary. Major concerns about potential health effects associated with inhalation of fugitive dusts from the red mud were investigated. Laboratory rodents were exposed via inhalation to red sludge dusts obtained from the field at high concentrations for 8 hours per day and for two-week duration. Following exposures, respiratory consequences on laboratory rodents were examined including histopathology to assess lung effects. Czovek (2011) concluded that inhalation of red sludge dust did not alter the basal respiratory mechanics, but it did lead to progression of mild airway hyper-responsiveness. Czovek (2011) further concluded that fine particles were able to reach the lower respiratory tract and induced mild inflammation around the alveoli and the pulmonary vasculature. The mild respiratory symptoms that developed following short-term exposure of healthy individuals to high concentrations of airborne red sludge dusts do not appear to pose a greater respiratory hazard than the inhalation of urban dust at a comparable concentration (Czovek 2011). Studies concluded that while there is high potential for re-suspension and alkalinity may cause irritation of the upper respiratory tract and eyes, based on its particulate size distribution and composition, red mud dust do not appear to pose a greater respiratory hazard than urban particulate matter (Gelencser 2011; Czovek 2011). No genotoxicity was observed using the resuspended dust collected from the field (Gelencser 2011; Gundy 2013).

The literature review did not identify any exposure limits or TRVs that can be used in this HHA to assess inhalation of bauxite residue.

6.2 REVIEW OF TOXICOLOGICAL BASIS OF AVAILABLE JURISDICTIONAL AMBIENT AIR EXPOSURE LIMITS FOR IDENTIFIED COPCS

Scientifically defensible long-term exposure limits applied in the HHA for each COPC were selected based on the following considerations:

- Established or derived by reputable and credible regulatory agencies;
- Derived based on human exposure studies;
- Derived based on chronic inhalation exposure or occupational studies;
- Year of primary study and toxicity review used to support the exposure limit;
- Protective of public health based on the current scientific understanding of the health effects known and/or suspected to be associated with exposures to the COPC;
- Protective of sensitive individuals through the use of appropriate uncertainty factors; and,
- Supported by adequate documentation.

In the case that the above criteria were supported by more than one standard, guideline or objective, the most scientifically defensible limit was selected and the rationale for the decision is provided in the toxicity profiles in **Appendix E.**

For constituents of bauxite residue and salt cake (identified COPCs), exposure limits or ambient air quality objectives used in the HHA were obtained from reputable regulatory agencies that regularly review and update the science supporting the exposure limits, provide supporting documentation, and/or engage a peer-review process in their standards development process. For the purposes of this HHA, these sources included:

- European Commission (EU) Air Quality Standards;
- United Kingdom (UK) Air Quality Limits;
- European Chemical Agency (ECHA) Evaluation, Authorisation and Restriction of Chemicals (REACH) Limits;
- World Health Organization (WHO) Global Air Quality Guidelines;
- California Ambient Air Quality Standards (CAAQS);
- Texas Commission on Environmental Quality (TCEQ) Effect Screening Levels (ESLs) and Air Monitoring Comparison Values (AMCVs); and
- American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV-TWA).

The EU, UK, WHO and CAAQS do not have exposure limits for the identified COPCs.

Exposure limits from the ECHA, TCEQ, and ACGIH and their toxicological basis are summarized for each COPC in the toxicological profiles provided in **Appendix E.**

6.3 TOXICOLOGICAL REVIEW OF IDENTIFIED COPCS

A complete toxicology review of associated health effects following inhalation exposures to the identified COPCs was also performed.

Toxicological information was summarized from the following sources, where available:

- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles;
- American Conference of Governmental Industrial Hygienists (ACGIH) Supporting Documents for TLVs;
- European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Toxicological Summaries;

— National Center for Biotechnology Information - PubChem Compound Summaries; and
— Texas Commission on Environmental Quality (TCEQ) Development Support Documents.

The health outcomes related to inhalation exposures to identified COPCs following short- and long-term exposures and the available human (or epidemiological) toxicological data are summarized in the toxicological profiles provided in **Appendix E.**

6.3.1 FINE PARTICULATE MATTER ($PM_{2.5}$)

Jurisdictional 24-hour and annual exposure limits for $PM_{2.5}$ are provided in **Table 6.1** and **Table 6.2,** respectively. The toxicological studies supporting these exposure limits are described in detail below.

Table 6.1 24-Hour Inhalation Exposure Limits for $PM_{2.5}$

Regulatory Agency	Type	Value (µg/m³)	Reference
Metro Vancouver	**24-hour**	**25**	**Metro Vancouver 2020**
BC MoECCS	**24-hour**	**25**	**BC MoECCS 2020**
AENV	24-hour	29	AENV AAQO 2018
CCME 2020 CAAQS	24-hour	27	CCME 2017
ON MECP	24-hour	27	Ontario MECP 2020
US EPA	24-hour	35	US EPA 2021
WHO	**24-hour**	**25**	**WHO 2005**

Notes:
BC MoECCS – British Columbia Ministry of Environment and Climate Change Strategy; AENV – Alberta Environment; CCME – Canadian Council of Ministers of Environment; ON MECP – Ontario Ministry of Environment, Conservation and Parks; US EPA – United States Environmental Protection Agency; Cal OEHHA - California Office of Environmental Health Hazard Assessment; WHO – World Health Organization

Metro Vancouver and British Columbia Ministry of Environment and Climate Change Strategy

The 24-hour Provincial air quality objective (AQO) is 25 µg/m³ and is based on annual 98th percentile of daily average, over one year. No technical supporting documents detailing the derivation of the AQO were made available. Metro Vancouver (2020) has also adopted this value and determines compliance based on a rolling average.

CCME

The CCME provides a 24-hour 2020 CAAQS for $PM_{2.5}$ (27 µg/m³); however, unlike other pollutants such as SO_2 and NO_2, a 2025 CAAQS is not provided for fine PM. CCME was consulted to obtain detailed rationale for the derivation of the CAAQS for fine PM; however, there was no technical documentation available. The report entitled: "*Guidance Document on Achievement Determination Canadian Ambient Air Quality Standards for Fine Particulate Matter and Ozone*" (CCME, 2020) provides guidance on methodologies for determining whether the CAAQS for PM are achieved or exceeded. However, it does not provide epidemiological studies that support the 2020 CAAQS for $PM_{2.5}$.

Alberta Environment

Alberta Environment (AENV, 2019) issued a 1-hour and 24-hour AAQO of 80 µg/m³ and 29 µg/m³, respectively. The 1-hour value is intended for use in monitoring and reporting of the Ambient Air Quality Index. The 24-hour value is reported as being based on health effects (AENV, 2018). AENV (2018) outlines that exposure to fine PM may be associated with respiratory health effects including: reduced lung function, asthma, emphysema and bronchitis, or cardiovascular effects such as: angina, heart attacks and hypertension. Fine PM has also been linked with increased emergency room visits and hospitalizations. AENV (2018) also referenced a 2011 Health Canada report which identified a linear relationship between the concentration of $PM_{2.5}$ and the health response, with no

clear evidence of a threshold for effects. Beyond this information, it is unclear how AENV came to derive the 1-hour and 24-hour AAQOs.

Ontario Ministry of the Environment, Conservation and Parks

The Ontario MECP (MECP, 2020) provides a 24-hour AAQC for $PM_{2.5}$ of 27 µg/m^3. This value reflects the 3-year average of the annual 98th percentile of the daily 24-hr average concentrations and is based on the 2020 CAAQS value. While the MECP (2020) identifies that this numerical value is based on health endpoints, there were no technical supporting documents that provide rationale supporting the derivation of this AAQC. For more details, the MECP references a 2012 CCME document entitled "*Guidance Document on Achievement Determination Canadian Ambient Air Quality Standards for Fine Particulate Matter and Ozone*". However, the document only focuses on methodologies, criteria, and procedures for reporting on achievement of the CAAQS and makes no mention of how the CAAQS value was derived.

United States Environmental Protection Agency

In 2006, the 24-hour NAAQS for $PM_{2.5}$ was revised from 65 to 35 µg/m^3. This value is identified as a 98th percentile, averaged over 3 years. US EPA (2006) concluded that a 24-hour standard of 35 µg/m^3 would protect public health with an adequate margin of safety from serious health effects including premature mortality and hospital admissions for cardiorespiratory causes that are likely associated with short-term exposure to fine PM. In 2012, US EPA re-evaluated the 24-hour value of 35 µg/m^3 for fine PM and retained it as the current standard.

World Health Organization

The WHO (WHO, 2005) provided a 24-hour guideline for $PM_{2.5}$ of 25 µg/m^3. This value represents a 99th percentile of the distribution of daily values and is intended to protect against peaks of pollution that would lead to substantial excess morbidity or mortality. This value is largely based on published risk coefficients from multicentre studies and meta-analyses, which reported an average short-term mortality effect for PM_{10} of approximately 0.5% per 10 µg/m^3. This value is considered to provide a significant reduction in risks from acute exposure health effects such as short-term mortality.

Table 6.2 Chronic Annual Inhalation Exposure Limits for $PM_{2.5}$

Regulatory Agency	Type	Value (µg/m^3)	Reference
Metro Vancouver	Annual	8	Metro Vancouver 2020
BC MoECCS	Annual	8	BC MoECCS 2020
CCME 2020 CAAQS	Annual	8.8	CCME 2017
AENV	-	-	AENV AAQO 2019
ON MECP	Annual	8.8	Ontario MECP 2020
US EPA	Annual	12	US EPA 2021
Cal OEHHA	Annual	12	Cal OEHHA 2016
WHO	Annual	10	WHO 2005

Notes:
BC MoECCS – British Columbia Ministry of Environment and Climate Change Strategy; AENV – Alberta Environment; CCME – Canadian Council of Ministers of Environment; ON MECP – Ontario Ministry of Environment, Conservation and Parks; US EPA – United States Environmental Protection Agency; Cal OEHHA - California Office of Environmental Health Hazard Assessment; WHO – World Health Organization

Metro Vancouver and British Columbia Ministry of Environment and Climate Change Strategy

In 2009, BC MoECCS (2020) provided an annual AQO of 8 µg/m^3 for $PM_{2.5}$. No technical supporting documents detailing the derivation of the AQO were made available. Metro Vancouver has adopted the same AQO and evaluates compliance based on annual average of 1-hour concentrations, over one year.

CCME

The CCME provides an annual 2020 CAAQS for $PM_{2.5}$ (8.8 µg/m^3); however, unlike other pollutants such as SO_2 and NO_2, a 2025 CAAQS is not provided for fine PM. CCME was consulted to obtain detailed rationale for the derivation of the CAAQS for fine PM; however, there was no technical documentation available. The report entitled: "*Guidance Document on Achievement Determination Canadian Ambient Air Quality Standards for Fine Particulate Matter and Ozone*" (CCME, 2020) provides guidance on methodologies for determining whether the CAAQS for PM are achieved or exceeded. However, it does not provide epidemiological studies that support the 2020 CAAQS for $PM_{2.5}$.

Ontario Ministry of the Environment, Conservation and Parks

The MECP (2020) provides an annual AAQC of 8.8 µg/m^3 for $PM_{2.5}$. The value reflects a 3-year average of the annual average concentrations. While the MECP identifies that this numerical value is based on health endpoints, there were no technical supporting documents that provide rationale supporting the derivation of this AAQC. For more details, the MECP references a 2012 CCME document entitled "Guidance Document on Achievement Determination Canadian Ambient Air Quality Standards for Fine Particulate Matter and Ozone". However, the document only focuses on methodologies, criteria, and procedures for reporting on achievement of the CAAQS and makes no mention of how the CAAQS value was derived.

United States Environmental Protection Agency

In 2013, US EPA revised the annual NAAQS for $PM_{2.5}$ from 15 to 12 µg/m^3, a value identified as an annual arithmetic mean, averaged over 3 years. Growing evidence since the last review showed that a lowering of the 15 µg/m^3 standard (originally set in 1997) was warranted given the multiple, multi-city studies over long periods of time demonstrating clear evidence of premature death, cardiovascular and respiratory harm as well as reproductive and developmental harm at concentrations below 15 µg/m^3. US EPA (2013) determined that an annual standard of 12 µg/m^3 is below the long-term mean $PM_{2.5}$ concentrations reported in each of the key multi-city, long- and short-term exposure studies that identified numerous serious health effects such as premature mortality and increased hospitalization for cardiovascular and respiratory effects. Additionally, a standard of 12 µg/m^3 considers the evidence of reproductive and developmental effects such as infant mortality and low birth weight which were identified in studies that provided evidence suggestive of a causal relationship with long-term $PM_{2.5}$ concentrations. A level of 12 µg/m^3 is approximately the same level as the lowest long-term mean concentration reported in these studies. US EPA (2013) concluded that an annual standard of 12 µg/m^3 provides the requisite degree of public health protection including the health of sensitive populations, with an adequate margin of safety.

California Office of Environmental Health Hazard Assessment

Cal OEHHA recommended an annual CAAQS of 12 µg/m^3 for $PM_{2.5}$, which places significant weight on the long-term exposure studies using the American Cancer Society (ACS) and Harvard Six-Cities data. In both studies, robust associations were identified between long-term exposure to $PM_{2.5}$ and mortality; the mean $PM_{2.5}$ concentrations were 18 and 18.2 µg/m^3 in the Harvard and ACS studies, respectively. In addition, the annual CAAQS placed weight on the results of multiple studies investigating the relationship between $PM_{2.5}$ and adverse health outcomes. These studies had long-term (three- to four-year) means in the range of 13 to 18 µg/m^3. It was concluded by Cal OEHHA (2001) that an annual $PM_{2.5}$ standard of 12 µg/m^3 would provide adequate public health protection, including that of infants and children, against adverse effects of long-term exposure.

World Health Organization

An annual average guideline value of 10 µg/m^3 for $PM_{2.5}$ was set by WHO (2005) to represent the lower end of the range over which significant effects on survival have been observed in the ACS study. This value also places significant weight on the long-term exposure studies using the ACS and Harvard Six Cities data which demonstrated

a robust association between long-term exposure to $PM_{2.5}$ and mortality (also discussed above). This annual standard is believed to be both achievable in large urban settings and is expected to effectively reduce health risks.

6.3.2 COARSE PARTICULATE MATTER (PM_{10})

Jurisdictional 24-hour and annual exposure limits for coarse particulates (PM_{10}) are provided in **Table 6.3**and **Table 6.4,** respectively. The toxicological studies supporting these exposure limits are described in detail below.

Table 6.3 24-Hour Inhalation Exposure Limits for PM_{10}

REGULATORY AGENCY	TYPE	VALUE (ppb)	VALUE (mg/m^3)	SOURCE
BC MoECCS	24-hour		5.0E-02	BC MoECCS 2020
AENV	-	-	-	AENV AAQO 2019
CCME 2020 (2025)	-	-	-	CCME 2019
ON MECP	24-hour	-	5.0E-02	Ontario MECP 2020
US EPA	24-hour	-	1.5E-01	US EPA 2021
Cal OEHHA	24-hour	-	5.0E-02	Cal OEHHA 2016
WHO	24-hour	-	5.0E-02	WHO 2005

Notes:
BC MoECCS – British Columbia Ministry of Environment and Climate Change Strategy; AENV – Alberta Environment; CCME – Canadian Council of Ministers of Environment; ON MECP – Ontario Ministry of Environment, Conservation and Parks; US EPA – United States Environmental Protection Agency; Cal OEHHA - California Office of Environmental Health Hazard Assessment; WHO – World Health Organization

British Columbia Ministry of Environment and Climate Change Strategy

A 24-hour AQO for PM_{10} was set to 50 $\mu g/m^3$ in 1995 and is the current provincial standard. BC MoECCS (2020) mentions that PM_{10} in this context includes both fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) fractions. No technical supporting documents detailing the derivation of the AQO were made available.

Ontario Ministry of the Environment, Conservation and Parks

A 24-hour AAQC for PM_{10} of 50 $\mu g/m^3$ was provided by the MECP (2020). The value is identified as an interim AAQC, with no conversion to other averaging times available. While the MECP identifies that this numerical value is based on health endpoints, there were no technical supporting documents that provide rationale supporting the derivation of this AAQC.

United States Environmental Protection Agency

The US EPA set a 24-hour NAAQS value for "thoracic coarse particles ($PM_{10-2.5}$)" of 150 $\mu g/m^3$ in 1987. The value is not to be exceeded more than once per year on average over a 3-year period. In 2013, as part of US EPA's (2013) review, it was concluded that the standard is sufficient to provide protection against effects associated with short-term exposure to coarse PM including premature mortality and increased hospital admissions and emergency department visits.

California Office of Environmental Health Hazard Assessment

The California Office of the Environmental Health Hazard Assessment (Cal OEHHA) derived a 24-hour California Ambient Air Quality Standard (CAAQS) of 50 $\mu g/m^3$ for PM_{10}. According to a Cal OEHHA (2001) staff report, this

standard was first promulgated in 1983, and was primarily based on an analysis of daily mortality in London, UK, in relation to changes in PM. In the following years, Cal OEHHA examined the increasing epidemiological studies that linked fluctuations in short-term PM_{10} with adverse health outcomes. Many of these studies had peak values close to or above 50 $\mu g/m^3$, with concentrations below 50 $\mu g/m^3$ having a more uncertain association with mortality effects. It was concluded that a 24-hour standard for PM_{10} at 50 $\mu g/m^3$ would offer public health protection primarily against peak concentrations of both fine and coarse PM.

World Health Organization

The World Health Organization (WHO, 2005) provided a 24-hour guideline for PM_{10} of 50 $\mu g/m^3$. These values represent a 99th percentile of the distribution of daily values and are intended to protect against peaks of pollution that would lead to substantial excess morbidity or mortality. The values are largely based on published risk coefficients from multicentre studies and meta-analyses, which reported an average short-term mortality effect for PM_{10} of approximately 0.5% per 10 $\mu g/m^3$. These values are considered to provide significant reductions in risks from acute exposure health effects such as short-term mortality.

Table 6.4 Chronic Inhalation Exposure Limits for PM_{10}

REGULATORY AGENCY	TYPE	VALUE (ppb)	VALUE (mg/m^3)	SOURCE
BC MoECCS	-	-	-	BC MoECCS 2020
AENV	-	-	-	AENV AAQO 2019
CCME 2020 (2025)	-	-	-	CCME 2021
ON MECP	-	-	-	Ontario MECP 2020
US EPA	-	-	5.0E-02 (revoked)	US EPA 2021
Cal OEHHA	Annual	-	2.0E-02	Cal OEHHA 2016
WHO	Annual	-	2.0E-02	WHO 2005

Notes:
BC MoECCS – British Columbia Ministry of Environment and Climate Change Strategy; AENV – Alberta Environment; CCME – Canadian Council of Ministers of Environment; ON MECP – Ontario Ministry of Environment, Conservation and Parks; US EPA – United States Environmental Protection Agency; Cal OEHHA - California Office of Environmental Health Hazard Assessment; WHO – World Health Organization

United States Environmental Protection Agency

An annual NAAQS for PM_{10} was set by the US EPA in 1987 at 50 $\mu g/m^3$. In a 2006 review by the US EPA, it was concluded that the annual PM_{10} standard would be revoked and not replaced, given that the available evidence does not suggest an association between long-term exposure to coarse PM at current ambient levels and health effects. In addition, the 24-hour PM_{10} (150 $\mu g/m^3$) was considered sufficient to provide adequate protection against any potential effects related to long-term exposure to PM_{10} concentrations.

California Office of Environmental Health Hazard Assessment

Cal OEHHA (2001) revised the annual CAAQS for PM_{10} from 30 to 20 $\mu g/m^3$. Adopting an annual standard at this level would place significant emphasis on ACS and Harvard Six-Cities studies examining mortality and morbidity related to long-term PM exposure. An overall PM mean of 30 and 18 $\mu g/m^3$ were assessed in the Harvard and ACS studies, respectively. It was determined by Cal OEHHA (2001) that a standard set at 20 $\mu g/m^3$ would protect against mortality effects related to long-term exposure in adults and morbidity effects such as acute bronchitis in children.

World Health Organization

An annual average guideline value of 20 $\mu g/m^3$ was set by WHO (2005). This value represents the lowest level at which total cardiopulmonary and lung cancer mortality have been shown to increase in the ACS study (although

there is more confidence in the $PM_{2.5}$ results from the study, which is why WHO preferred use of the $PM_{2.5}$ guideline). There is limited quantitative evidence on the long-term effects of coarse PM; however, there is significant literature investigating the short-term effects. For this reason, the literature on short-term effects has been used as a basis for development of the annual PM_{10} guideline value.

6.3.3 EXPOSURE LIMITS FOR IDENTIFIED COPCS

Jurisdictional 24-hour and annual exposure limits for identified COPCs are provided in **Table 6.5.** The toxicological studies supporting these exposure limits are described in detail below.

Table 6.5 Selected Exposure Limits or Toxicity Reference Values for Identified COPCs

COPC	TRV (mg/m^3)	SOURCE	BASIS
Aluminium Goethite	0.01	ACGIH 2008	**Respiratory and neurological effects** ACGIH established a TLV-TWA of 1 mg/m^3 for aluminium and its insoluble compounds (including aluminium oxide and aluminium in bauxite ore dust). The authors reviewed available literature and concluded that a urinary aluminium level of 100 µg/L (corresponding to an airborne concentration of 1.6 mg/m^3) was a critical concentration for development of neurological effects based on an occupational study by Sjogren and Elinder (1992). The study identified that long-term exposures to aluminium and aluminium compounds leading to body burdens equivalent to breathing 1.6 mg/m^3 for 40 years can result in an increased prevalence of neurological effects. An additional uncertainty factor of 100 was applied to the ACGIH limit to ensure protection of the public including sensitive individual from continuous exposures. The resulting exposure limit of 0.01 mg/m^3.
Aluminium Oxide	0.01	ACGIH 2008	**Respiratory and neurological effects** See Aluminium Goethite
Anatase and Rutile *(also known as titanium dioxide)*	0.01	ACGIH 2001	**Respiratory irritation** ACGIH derived a TLV-TWA of 10 mg/m^3 for titanium dioxide. The TLV-TWA was based on Lee *et al.* (1986), who conducted a 2-yr inhalation study on rats exposed to titanium dioxide at concentrations of 0, 10, 50, or 250 mg/m^3 for 6 hrs/day, 5 days/week. Squamous cell carcinomas developed following exposure to 250 mg/m^3 for the full 2 years. At 50 mg/m^3, massive accumulations of macrophages and foamy dust cells were reported which were indicative of pulmonary air-space overload. At 10 mg/m^3, a particulate (insoluble) not otherwise specified (PNOS) response was observed, whereby the architecture of the air spaces were unchanged, there was no significant formation of scar tissue, and the tissue reaction was potentially revisable. The TLV-TWA of 10 mg/m^3 is intended to protect against respiratory tract irritation, and potential overload of pulmonary air-space architecture and normal clearance mechanisms. An additional uncertainty factor of 1000 was applied to the ACGIH limit for animal to human uncertainty and to ensure protection of the public including sensitive individuals from continuous exposures. The resulting exposure limit of 0.01 mg/m^3 is applied in this HHA.
Arsenic Trioxide	0.000067	TCEQ 2013	**Respiratory and lung cancer** TCEQ developed a long-term ESL/AMCV of 0.000067 mg/m^3 for arsenic trioxide based on lung cancer mortality rates associated with inhalation of inorganic arsenic compounds. The ESL/AMCV was derived from Lubin *et al.* (2008), an occupational study looking at excess lung cancer mortality for all workers adjusting for year of hire. The study used Texas-specific mortality rates for 2001-2005 from lung cancer and Texas-specific survival rates for 2005. Texas air concentrations corresponding to an excess cancer risk of 1 in 100,000 based on the final URF of 1.5E-04 per $\mu g/m^3$ was selected as the ESL/AMCV (TCEQ, 2013).

COPC	TRV (mg/m^3)	SOURCE	BASIS
Boehmite *(also known as Aluminium oxide hydroxide)*	0.01	ACGIH 2008	**Respiratory and neurological effects** See Aluminium Goethite
Calcium Cancrinite	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Cerium Oxide	0.005	TCEQ 2021	TCEQ adopted a long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Chromium Trioxide	0.0000043	TCEQ 2014	**Lung Cancer** TCEQ developed a long-term AMCV of 0.0000043 mg/m^3 for chromium trioxide based on hexavalent chromium particulate compounds (including chromium trioxide). The AMCV was derived from Crump at al. (2003) and Gibb *et al*. (2000), epidemiological studies that looked at the association between CrVI exposure and lung cancer in chromate production worker cohorts in Ohio and Maryland, USA. These cohorts are relatively large, have extensive follow-up, and documentation of historical CrVI exposure levels. The Crump (2003) study included 482 workers employed for at least one-year from1940 to 1972 and followed through 1997 (14,443 person-years). Cumulative exposure to CrVI was significantly associated with increased lung cancer risk. The Gibb (2000) study evaluated lung cancer mortality in a cohort of 2,357 male chromate production workers in Baltimore, Maryland hired during 1950 to1974, with mortality followed through 1992. The long-term AMCV was calculated based on an inhalation unit risk factor (URF) of 2.3 × 10-3 per $\mu g/m^3$ derived from these studies and a no significant risk level of 1 in 100,000 excess cancer risk.
Copper Oxide	0.001	ACGIH 2001	**Ocular, dermal, respiratory tract and mucous membrane irritation** ACGIH derived a TLV-TWA of 1 mg/m^3 for copper dusts (including copper oxide) and 0.2 mg/m^3 for copper misits. Several studies were used to support this value. Whitman (1957) found that exposure to concentrations of copper fume between 0.02 to 0.4 mg/m^3 for short periods from welding operations did not cause any complaints. Gleason (1968) identified a condition similar to metal fume fever in workers exposed to metallic copper dust at concentrations of 0.1 mg/m^3. Finally, data from industry, specifically for copper-welding operations and copper-metal refining in Great Britain (Luxon S.G, 1972) supports the view that no adverse effects develop from exposure to fumes up to 0.4 mg/m^3 of copper. No further discussion on the derivation of the TLV-TWA was available. The TLV-TWA values are intended to protect against ocular, dermal, respiratory tract, and mucous membrane irritation. A safety factor of 1000 was applied to the ACGIH limit to account for acute to chronic exposure uncertainty and to ensure protection of the public from continuous exposures, resulting in a final exposure limit of 0.001 mg/m^3.
Gallium Trioxide	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity

COPC	TRV (mg/m^3)	SOURCE	BASIS
Gypsum *(also known as calcium sulfate dihydrate)*	0.01	ACGIH 2006	**Respiratory tract irritation** ACGIH derived a TLV-TWA of 10 mg/m^3 for calcium sulphate (including the dihydrate). The TLV-TWA was derived from Cain *et al*. (2004). who exposed 12 individuals to varying concentrations of calcium sulphate (10, 20, and 40 mg/m^3) during exercise for a total of 20 minutes. It was reported that chemesthetic effects on the nose and throat were present only at the 40 mg/m^3 level; no effects to the eye, nasal secretion, nasal resistance, or mucociliary transport were observed at the other exposure levels. Although limited data exists, a TLV-TWA of 10 mg/m^3 is recommended based on lowest exposure dose in the Cain (2004) study to protect against long-term respiratory health effects as demonstrated in both animal and human studies following exposure to calcium sulphate. An additional safety factor of 1000 was applied to the ACGIH limit for acute to chronic exposure uncertainty and to ensure protection of the public from continuous exposures, resulting in a final exposure limit of 0.01 mg/m^3.
Hematite (also known as iron oxide)	0.05	ACGIH 2006	**Non-specific inflammatory responses; pulmonary siderosis** An ACGIH review derived a TLV-TWA of 5 mg/m^3 (respirable particulate mass) for iron oxide. The TLV-TWA is based on several experimental human and animal studies (Keenan K *et al*, 1989; Lay JC *et al*, 1999) which have demonstrated that instillation of iron oxide into the lungs caused a mild inflammatory response but showed no evidence of fibrogenic potential. Pulmonary siderosis has been identified in chest X-rays associated with deposition and collection of iron oxide in the lungs from relatively high level (10-700 mg/m3) exposures for prolonged periods based on occupational exposures (Jones *et al*., 1972 and Teculescu *et al*., 1973). Additionally, an inhalation study in rabbits (Grant MM *et al*, 1979) demonstrated that iron oxide increased the number of lavagable pulmonary macrophages at about 200 mg/m3 and increased phagocytic activity at 20 mg/m3 for 2 hrs. Limited discussion is available as to how the specific TLV-TWA was derived from these studies. The TLV-TWA-TWA of 5 mg/m3 is recommended for occupational exposure to iron oxide to minimize the potential for nonspecific inflammatory responses and development of x-ray changes in the lung. An additional safety factor of 100 was applied to the ACGIH limit to ensure protection of the public including sensitive individuals from continuous exposures, resulting in a final exposure limit of 0.05 mg/m^3.
Hydrogarnet	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Lead Oxide	0.00015	TCEQ 2021	**IQ loss in children** TCEQ adopted a long-term ESL/AMCV for lead oxide from the NAAQS value for lead of 0.15 $\mu g/m^3$, which is not to be exceeded over a 3-month rolling average. The limit was derived by the NAAQS using estimated mean IQ loss for children in the USA related to lead concentrations in air. Under the air-to-blood ratio of 1:7, the air-related IQ loss is below 2-points at lead concentrations of 0.15 ug/m3 (US EPA, 2008). The US EPA reviewed these criteria in 2016 and decided to retain the value with no revisions.

COPC	TRV (mg/m^3)	SOURCE	BASIS
Manganese Oxide	0.00084	TCEQ 2017	**Abnormal eye-hand coordination scores in humans** TCEQ developed a long-term AMCV of 0.84 $\mu g/m^3$ for manganese and inorganic manganese compounds (including manganese oxide). The AMCV was derived from Roels *et al*. (1992), an occupational study with 92 male workers in a dry alkaline battery factory. Total and respirable Mn dust concentrations were measured using personal air sampling in different occupational areas within the factory. Workers were exposed for an average duration of 5.3 years (range 0.2-17.7 years) to average (geometric mean) concentrations of 0.215 and 0.948 mg Mn/m3 in respirable and total dust, respectively. The BMDL10 based on abnormal eye-hand coordination scores was selected as the point of departure (POD), adjusted for continuous exposure. An uncertainty factor (UF) of 10 was applied to account for intrahuman variability and 6 for limitations and uncertainties in the database, including lack of epidemiological data for humans chronically exposed to soluble forms of Mn and lack of developmental studies.
Niobium Pentoxide	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Perovskite *Also known as calcium titanium trioxide	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Sodium Fluoride	0.027	TCEQ 2015	**Increased bone density and skeletal fluorosis** TCEQ developed a long-term ESL of 8.1 $\mu g/m^3$ for soluble inorganic fluorides (including sodium fluoride). The ESL was derived from Derryberry *et al*. (1963), which was an occupational study where fluoride exposure levels, urinary monitoring, and the health effects from fluoride were evaluated on 74 male workers in a fertilizer manufacturing plant. The length of employment for these workers ranged from 4.5 to 25.9 years (average 14.1 years) with 76% of workers having over 10 years of employment. The $BMCL_{10}$ for increased bone density and skeletal fluorosis was selected as the point of departure (POD). The POD was adjusted for continuous exposure and non-occupational ventilation rates. An uncertainty factor (UF) of 10 was applied to account for human variability. An UF of 1 was used for database uncertainty because human studies investigating a wide range of health endpoints were available and the overall quality of the key studies is high. It was not necessary to incorporate a UF to adjust for the use of a sub chronic study since the average exposure duration of 14.1 years is more than 10% of the life span in humans. Therefore, the study was considered chronic.
Sodium Oxalate	0.01	ACGIH 2015	**Eye, skin, and upper respiratory tract irritation based on acidity** ACGIH derived a TLV-TWA of 1 mg/m^3 for oxalic acid (surrogated by to sodium oxalate). Leung and Paustenbach (1990) examined the irritancy potential for several carboxylic acids by studying the correlation between TLV-TWA values and acid dissociation constants, given that acidity is considered the principal factor in the irritancy potential for many carboxylic acids. The acids examined typically have a TLV-TWA basis of upper respiratory and eye irritation. After plotting the TLV-TWA values for a range of carboxyclic acids, a model was used to determine the TLV-TWA of oxalic acid, which resulted in a TLV-TWA of 1.05 mg/m^3. The TLV-TWA of 1 mg/m^3 is intended to protect against eye, skin, and upper respiratory tract irritation. An additional safety factor of 100 was applied to the ACGIH value for uncertainty related to the use of oxalic acid as a surrogate, and to ensure protection of the public including sensitive individuals from continuous exposures.

COPC	TRV (mg/m^3)	SOURCE	BASIS
Sodium Sulphate	0.005	ACGIH 2001	**Eye, skin, mucous membrane, and respiratory tract irritation** ACGIH derived a TLV-TWA-TWA of 5 mg/m^3 for sodium bisulfate (used as surrogate by WSP for sodium sulphate). The basis for deriving the TLV-TWA was not provided; however, it was recommended that a TLV-TWA of 5 mg/m^3 be adopted to minimize the potential for eye, skin, mucous membrane, and respiratory tract irritation. A safety factor of 1000 was applied to the ACGIH limit to account for uncertainty related to the use of sodium bisulphate as a surrogate for sodium sulphate, the limited details on the supporting study or derivation by ACGIH, and to ensure protection of the public from continuous exposures.
Strontium Oxide	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Thorium Oxide	0.005	TCEQ 2021	Applied the TCEQ long-term ESL of 0.005 mg/m^3 based on the general ESL for metals with low toxicity
Vanadium Pentoxide	0.0005	ACGIH 2009	**Upper and lower respiratory tract irritation** ACGIH identified a TLV- TWA of 0.05 mg/m^3 for vanadium pentoxide. The TLV-TWA was based on human data from Kiviluoto (1979). The study showed that subjects exposed to 0.2-0.5 mg V/m^3 measured as total dust for 11 years in the vanadium industry did not develop any upper respiratory symptoms but did show increased leuocytes (from nasal biopsy results) and self reported wheezing when compared to a referent group. The differences in nasal biopsy results were resolved after exposure was reduced to 0.01 to 0.04 mg V/m^3 as total dust. The study supports a TLV-TWA of 0.02 to 0.08 mg/m^3 (adjusted inhalable) that is not associated with nasal changes. A TLV-TWA of 0.05 mg/m^3 represents the adjusted mean of the no effect range considered to be protective of airway inflammatory changes from exposure to vanadium pentoxide. A safety factor of 100 was applied by WSP to the ACGIH limit to ensure protection of the public from continuous exposures, resulting in a final exposure limit of 0.0005 mg/m^3.
Yttrium Trioxide	0.001	ACGIH 2001	**Respiratory fibrosis** ACGIH derived a TLV-TWA of 1 mg/m^3 for yttrium and its compounds. The TLV-TWA value is intended to protect against respiratory fibrosis, as reported in rats by Mogilevskaya O.Y and Rakhlin N.T (1963). The study administered a single 50 mg dose of yttrium intratracheally to rats and sacrificed the animals 8 months later. The rats developed pulmonary changes, including increased lung weight, diffuse fibrosis, and emphysema. No further information was available as to how the TLV-TWA was derived from this study. ACGIH noted that toxicity data and industrial evidence reports for exposure to yttrium or its compounds are limited. A safety factor of 1000 was applied by WSP to the ACGIH limit for acute to chronic exposure uncertainty, animal to human uncertainty, and to ensure protection of the public from continuous exposures, resulting in a final exposure limit of 0.001 mg/m^3.
Zinc Oxide	0.0024	TCEQ 2021	**Lung function disorders; asthmatic symptoms** TCEQ adopted the long-term ESL/AMCV of 2.4 $\mu g/m^3$ for zinc oxide based on the German MAK for zinc of 2.4 mg/m^3 with an additional safety factor of 1000 (TCEQ, 2021). The MAK value was derived based on Roto (1980), an occupational study where 234 zinc ore smelting workers were exposed to 2.5 to 4.5 mg/m^3 of zinc oxide (as total dust with 90% zinc content) for an average of 5.5 years. No effects related to lung function disorders or asthmatic symptoms were observed across exposure groups. The NOAEL of 2.5 mg/m^3 was selected as the point of departure (POD) (DFG, 2014).

COPC	TRV (mg/m^3)	SOURCE	BASIS
Zircon	0.005	ACGIH 2001	**Respiratory irritation** ACGIH derived a TLV-TWA of 5 mg/m^3 for zirconium and its compounds (including zirconium silicate). The TLV-TWA is based on several studies. An animal inhalation study by Spiegl *et al*. (1956), where exposure to zirconium tetrachloride at a concentration of 6 mg Zr/m^3 for two months was associated with a small increase in mortality of rats and guinea pigs and no increased mortality for rabbits, cats, or dogs. Respiratory infection was the cause of death. Also, two 1-yr animal inhalation studies (Stokinger H.E, 1981; Hodge H.C, 1955) where exposure to zirconium tetrachloride at 3.5 mg/m^3 resulted in no adverse effects. The TLV- TWA of 5 mg/m^3 is intended to protect against respiratory irritation. An additional safety factor of 1000 was applied to the ACGIH limit to account for animal to human uncertainty and to ensure protection of the public including sensitive individuals from continuous exposures.

6.4 UNCERTAINTY ANALYSIS

The major sources of uncertainty associated with the Hazard Assessment stage of the HHA are briefly described below:

6.4.1 COPCS WITH NO AVAILABLE LIMITS

There are no available exposure limits for calcium cancrinite, cerium oxide, gallium trioxide, hydrogarnet, niobium pentoxide, perovskite, strontium oxide and thorium oxide. The uncertainty for each of these COPCs is discussed below.

Calcium Cancrinite, Gallium Trioxide, Hydrogarnet, Perovskite, Strontium Oxide

There is no toxicity information found for these COPCs in the major toxicological databases (including ATSDR, ACGIH, ECHA, TCEQ or PubChem). There are also no hazard codes associated with these COPCs. These COPCs are therefore considered to pose low hazard and there is low uncertainty related to not quantitatively evaluating their potential risks. This HHA applied an exposure limit of 0.005 mg/m^3 adopted from TCEQ based on the general ESL for metals with low toxicity.

Cerium Oxide

TCEQ adopted a long-term health-based ESL of 0.005 mg/m^3 for cerium oxide based on the general ESL for metals with low toxicity. This value was selected as the TRV for the HHA as it was the only available exposure limit for cerium oxide. As part of the ECHA REACH for cerium oxide, it was concluded that the chemical was not considered acutely or chronically toxic to humans. There are also no hazard codes listed for cerium oxide. Medium uncertainty is associated with the use of TCEQ limit, and this limit likely overestimates potential risk from cerium oxide.

Niobium Pentoxide

Hazard codes associated with niobium pentoxide include skin irritation, eye irritation and respiratory irritation. However, these hazards are typically associated with acute exposures which is evaluated in this HHA in consideration of particulate matter concentrations **(**refer to **Section 7).**

With respect to chronic exposures, ECHA REACH for niobium pentoxide listed a repeated oral dose study, where niobium pentoxide was administered in deionised water to the male (28-29 days) and female (maximum 54 days) rats at dosages of 250, 500 and 1000 mg/kg. There were no major toxicological findings. Given that the NOAEL is greater than 1000 mg/kg body weight in males and females, ECHA REACH concluded that toxicological testing from other routes of exposure was not necessary. Further ECHA REACH concluded that niobium pentoxide was not genotoxic or mutagenic.

Niobium pentoxide is therefore considered to pose low hazard and there is low uncertainty related to not quantitatively evaluating its potential risks. This HHA applied an exposure limit of 0.005 mg/m^3 adopted from TCEQ based on the general ESL for metals with low toxicity.

Sodium Oxalate

The exposure limit for oxalic acid is surrogated to sodium oxalate as there was no toxicity information or exposure limits related to inhalation or irritation identified for sodium oxalate. The only hazard codes for sodium oxalate are associated with oral exposures. The exposure limit for oxalic acid is based on the relationship between acidity and irritation of carboxylic acids. As sodium oxalate is considered neutral, the use of oxalic acid as a surrogate likely overestimates potential risks.

Sodium Sulphate

The exposure limit for sodium bisulphate is surrogated to ACGIH's limit for sodium sulphate as there was no toxicity information or exposure limits identified for sodium sulphate. The toxicological basis for the sodium

bisulphate exposure limit was not provided by ACGIH. The TCEQ limit for sodium sulphate is surrogated to particulate matter, as TCEQ determined that for species of limited concern the determination of the individual species impacts is not required. There are also no hazard codes associated with sodium sulphate. There is medium uncertainty with the use of the ACGIH limit and it likely overestimates potential risk associated with sodium sulphate.

Strontium Oxide

TCEQ adopted a long-term health-based ESL of 0.005 mg/m^3 for strontium oxide based on the general ESL for metals with low toxicity. This value was selected as the TRV for the HHA as it was the only available exposure limit for strontium oxide. There is limited information related to the toxicological effects from inhalation of strontium oxide, although the hazard code for causing severe skin burns and eye damage is listed. These hazards are typically associated with acute exposures, which is evaluated in this HHA in consideration of particulate matter concentrations **(**See **Section 6.1).** There is medium uncertainty with the use of the TCEQ limit.

Thorium Oxide

Hazard codes associated with thorium oxide include toxic if swallowed, toxic in contact with skin, toxic if inhaled, may cause cancer, and may cause damage to organs.

Studies on thorium workers have shown that breathing dust containing thorium and other substances may damage the lung many years after being exposed. Sufficiently high exposure may also change the genetic material of those body cells where the thorium is deposited. One study showed that working in a thorium plant increased the chance of death in males; but decreased the chance of death in females. Increasing the amount of thorium in your environment could increase your exposure to radium and radon. Therefore, it has not been determined whether the adverse health effects associated with exposure to thorium are the result of the ionizing radiation, the chemical toxicity of thorium, or a combination of radiation and chemical toxicity (ATSDR, 2019)

Further, thorium was once thought to have caused cancer in mine and mill workers, but it was later concluded that thorium likely had no significant impact on their cancer risk. Cancers in those workers were likely due to their cigarette smoking and inhaling silica dust. Thorium is mildly radioactive (has a very long half-life) so health effects from exposure may be partly from the chemical itself and partly from the radiation it emits. IARC has not found sufficient evidence to classify thorium in mines and mills as carcinogenic. NTP considers that thorium dioxide can cause cancer if it is injected into the body, as in medical procedure rather than inhaled. The carcinogenicity of thorium has not been evaluated in laboratory animals following inhalation (ATSDR, 2019). In absence of available TRVs from regulatory agencies, this HHA applied an exposure limit of 0.005 mg/m^3 adopted from TCEQ based on the general ESL for metals with low toxicity.

6.4.2 USE OF OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits from ACGIH were considered for this assessment. ACGIH provides TLVs to evaluate potential workplace health hazards from inhalation and these are preferentially based on human epidemiological studies. TLV-TWAs are protective of exposures from an 8-hour workday, 40-hr work week, that nearly all workers may be repeatedly exposed to over a working lifetime without adverse effects. These values are typically comparted to the average concentration measured over a workday. To ensure protection of the general population (including sensitive individuals such as asthmatics, children, and elderly) from continuous exposure, an additional uncertainty factor of 100 to 1000 were applied. This maintains a conservative approach that errs on the side of caution and likely overestimates predicted risks.

7 RISK CHARACTERIZATION

Risk characterization is the final step in the HHA process, during which the exposure and hazard (toxicity) assessments are integrated. The process of risk characterization conducted in this HHA reflects the conservative approach used to generate risk estimates. The process and interpretation of these steps are discussed in the following sections. Key uncertainties that influence results, including data gaps, are also described.

7.1 QUANTIFYING HAZARDS FOR NON-CARCINOGENIC CHEMICALS OF POTENTIAL CONCERN

For identified COPCs with associated non-carcinogenic health effects, the potential for exposures to result in harmful human health effects is based on the ratio between the estimated exposure and health-based exposure limits. This ratio is called the Exposure Ratio (ER) or Hazard Quotient (HQ) and is calculated as shown below. The HQ provides an indication of whether estimated exposures are large enough to be of concern for human health. Typically, a HQ of less than 1 indicates that exposures would not be expected to result in adverse human health effects. Given that conservative assumptions are used by regulatory agencies in the development of toxicity values and/or health-based exposure limits, HQ values greater than 1.0 do not mean that adverse human health effects will occur, but the likelihood that an adverse effect will occur increases as the HQ value rises above 1.0

$$HQ = \frac{EE}{TRV}$$

Where:

HQ = Hazard Quotient (unitless)

EE = Exposure Estimate (µg/m^3)

TRV = Chemical-Specific Toxicological Reference Value (µg/m^3)

It should be noted that EE is derived differently for short-term (24-hour) versus chronic (annual) exposures. For chronic exposures, EE is defined as the annual mean air concentration (with adjustment for hours of exposure and averaging time for each receptor group) because the timeframe of interest is related to longer term annual exposures.

The equation used to derive the chronic (annual) EE is presented below:

$$EE_{chronic\ (annual)} = C_{air} \times ET \times EF \times ED/AT$$

Where:

C_{air} = Modelled concentration of contaminant in air (µg/m^3);

ET = Exposure time (hours/day);

EF = Exposure frequency (days/year);

ED = Exposure duration (years); and,

AT = Averaging time (days)

A HQ benchmark of 1.0 was applied for residents who live near the Project. The HQ benchmark of 1.0 is applicable when baseline exposure is considered in the exposure assessment and all sources of exposure are evaluated. This assumption is considered met for the resident receptors/exposure scenarios.

A HQ benchmark of 0.2 was applied for the following receptors: students attending the primary school and teachers who work at the school. The HQ benchmark of 0.2 is applicable in these cases because these receptors may receive only a portion of their theoretical exposure within the HHA study area. The lower HQ benchmark allows for exposures outside of those considered in this assessment.

7.2 QUANTIFYING INCREMENTAL LIFETIME RISKS FOR CARCINOGENIC CHEMICALS

Carcinogenic chemicals are generally considered to elicit health effects from a non-threshold mechanism. This means that there is no dose below which an adverse effect will not occur. Any exposure to a carcinogen is considered to be associated with some level of risk. For carcinogenic chemicals, the potential for exposures to result in harmful effects is based on the Incremental Lifetime Cancer Risk (ILCR). For this assessment, the ILCR is calculated as follows:

$$ILCR = \frac{EE}{TRV}$$

Where:

ILCR = Incremental Lifetime Cancer Risk (Unitless)

EE = Exposure Estimate ($\mu g/m^3$)

TRV = Chemical-Specific Toxicological Reference Value ($\mu g/m^3$)

Estimates of non-threshold cancer risk are based on the lifetime probability of developing cancer because of environmental exposure to a carcinogenic substance. An ILCR represents the increased probability of an individual developing cancer over a 78-year lifespan because of exposure to a carcinogenic COPC associated with the Project (i.e., incremental risk above the typical background risk that exists).

7.1.1.1 *RESULTS OF THE NON-CARCINOGENIC ASSESSMENT*

Table 7.1 and **Table 7.2** present the predicted health risks associated with exposures to background levels of PM_{10} and $PM_{2.5}$ for students and teachers at the primary school and nearby residents, respectively. It is noted that there are no health concerns related to background PM_{10} and $PM_{2.5}$ for all receptors as indicated by the calculated HQs.

Table 7.1 Predicted Health Risks Associated with Exposure to Background Levels of PM_{10} and $PM_{2.5}$ for School Receptors

PARTICULATE MATTER (PM)	BACKGROUND CONC. (mg/m^3)	ADJUSTED BACKGROUND CONC. (mg/m3)	HQ (BASELINE)
PM_{10} (24-hr)	1E-02	Child: 2E-03 Teen: 5E-04 Adult: 3E-03	Child: 4E-02 Teen: 1E-02 Adult: 5E-02
PM_{10} (Annual)			Child: 5E-02 Teen: 1E-02 Adult: 6E-02
$PM_{2.5}$ (24-hr)	7E-03	Child: 1E-03 Teen: 3E-04 Adult: 2E-03	Child: 5E-02 Teen: 1E-02 Adult: 6E-02
$PM_{2.5}$ (Annual)			Child: 6E-02 Teen: 1E-02 Adult: 7E-02

Notes:
Target HQ = 0.2
HQs presented in **bold** if Target HQ is exceeded
Value in brackets represents averaging period
HQ values between 24-hr and annual PM differ given the different TRVs used for each averaging period

Table 7.2 Predicted Health Risks Associated with Exposure to Background Levels of PM_{10} and $PM_{2.5}$ for Nearby Residential Receptors

PARTICULATE MATTER (PM)	BACKGROUND CONC. (mg/m^3)	ADJUSTED BACKGROUND CONC. (mg/m^3)	HQ (BASELINE)
PM_{10} (24-hr)	1E-02	All resident life stages: 9E-03	All resident life stages: 2E-01
PM_{10} (Annual)		All resident life stages: 9E-03	All resident life stages: 2E-01
$PM_{2.5}$ (24-hr)	7E-03	All resident life stages: 6E-03	All resident life stages: 2E-01
$PM_{2.5}$ (Annual)		All resident life stages: 6E-03	All resident life stages: 3E-01

Notes:
Target HQ = 1
HQs presented in **bold** if Target HQ is exceeded
Value in brackets represents averaging period
"All resident life stages" represents each of the individual life stages, separately (i.e., infant, toddler, child, teen, and adult life stages)
Annual PM values were assessed for lifetime receptor, whereas 24-hr values were assessed for each individual life stage

Table 7.3 presents the predicted health risks associated with exposures to identified COPCs for students and teachers at the nearby primary school. The results of the quantitative risk analysis indicate that there are no health concerns for all receptors (as indicated by the calculated HQs for identified COPCs). However, it is noted that the summed HQ resulting from potential exposures to Project plus Background ambient concentrations is primarily attributable to exposures by background and drives over 60% of the predicted health risks.

Table 7.3 Predicted Health Risks Associated with Potential Exposure to Bauxite Residue and Salt Cake COPCs in PM_{10} (24-hr) for School Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Aluminum Goethite	9.8E-04	Child: 1.9E-04 Teen: 4.8E-05 Adult: 2.4E-04	Child: 1.9E-02 Teen: 4.8E-03 Adult: 2.4E-02	Child: 5.8E-02 Teen: 1.5E-02 Adult: 7.3E-02	Child: 67% Teen: 65% Adult: 67%
Hematite	8.8E-04	Child: 1.7E-04 Teen: 4.3E-05 Adult: 2.2E-04	Child: 3.4E-03 Teen: 8.6E-04 Adult: 4.3E-03	Child: 4.5E-02 Teen: 1.1E-02 Adult: 5.3E-02	Child: 92% Teen: 92% Adult: 92%
Anatase and Rutile	1.9E-04	Child: 3.8E-05 Teen: 9.4E-06 Adult:4.8E-05	Child: 3.8E-03 Teen: 9.4E-04 Adult: 4.8E-03	Child: 4.3E-02 Teen: 1.1E-02 Adult: 5.4E-02	Child: 91% Teen: 92% Adult: 91%
Boehmite	1.0E-04	Child: 2.0E-05 Teen: 4.9E-06 Adult: 2.5E-05	Child: 2.0E-03 Teen: 4.9E-04 Adult: 2.5E-03	Child: 4.1E-02 Teen: 1.0E-02 Adult: 5.1E-02	Child: 95% Teen: 95% Adult: 95%
Zircon	1.4E-05	Child: 2.8E-06 Teen: 6.9E-07 Adult: 3.5E-06	Child: 5.5E-04 Teen: 1.4E-04 Adult: 7.0E-04	Child: 4.0E-02 Teen: 9.9E-03 Adult: 5.0E-02	Child: 99% Teen: 99% Adult: 99%
Gypsum	7.1E-06	Child: 1.4E-06 Teen: 3.4E-07 Adult: 1.7E-06	Child: 1.4E-04 Teen: 3.4E-05 Adult: 1.7E-04	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.6% Teen: 99.7% Adult: 99.6%
Sodium Sulphate	3.5E-06	Child: 6.9E-07 Teen: 1.7E-07 Adult: 8.7E-07	Child: 1.4E-04 Teen: 3.4E-05 Adult: 1.7E-04	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.6% Teen: 99.7% Adult: 99.6%
Sodium Fluoride	9.4E-07	Child: 1.8E-07 Teen: 4.6E-08 Adult: 2.3E-07	Child: 6.8E-06 Teen: 1.7E-06 Adult: 8.6E-06	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Chromium Trioxide	9.4E-06	Child: 1.8E-06 Teen: 4.6E-07 Adult: 2.3E-06	Child: 1.4E-03 Teen: 3.5E-04 Adult: 1.8E-03	Child: 4.0E-02 Teen: 1.0E-02 Adult: 5.1E-02	Child: 97% Teen: 97% Adult: 97%
Vanadium Pentoxide	9.4E-06	Child: 1.8E-06 Teen: 4.6E-07 Adult: 2.3E-06	Child: 3.7E-03 Teen: 9.2E-04 Adult: 4.6E-03	Child: 4.3E-02 Teen: 1.1E-02 Adult: 5.4E-02	Child: 91% Teen: 91% Adult: 91%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Manganese Oxide	1.6E-06	Child: 3.2E-07 Teen: 8.0E-08 Adult: 4.1E-07	Child: 3.8E-04 Teen: 9.6E-05 Adult: 4.8E-04	Child: 3.9E-02 Teen: 9.9 E-03 Adult: 4.9E-02	Child: 99% Teen: 99% Adult: 99%
Zinc Oxide	2.4E-07	Child: 4.6E-08 Teen: 1.1E-08 Adult: 5.8E-08	Child: 1.9E-05 Teen: 4.8E-06 Adult: 2.4E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Lead Oxide	3.3E-07	Child: 6.4E-08 Teen: 1.6E-08 Adult: 8.1E-08	Child: 4.3E-04 Teen: 1.1E-04 Adult: 5.4E-04	Child: 3.9E-02 Teen: 9.9E-03 Adult: 5.0E-02	Child: 99% Teen: 99% Adult: 99%
Yttrium Trioxide	4.5E-07	Child: 8.7E-08 Teen: 2.2E-08 Adult: 1.1E-07	Child: 8.7E-05 Teen: 2.2E-05 Adult: 1.1E-04	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.8% Teen: 99.8% Adult: 99.8%
Copper Oxide	1.9E-07	Child: 3.7E-08 Teen: 9.2E-09 Adult: 4.6E-08	Child: 3.7E-05 Teen: 9.2E-06 Adult: 4.6E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Strontium Oxide	4.5E-07	Child: 8.7E-08 Teen: 2.2E-08 Adult: 1.1E-07	Child: 1.7E-05 Teen: 4.4E-06 Adult: 2.2E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Cerium Oxide	9.4E-07	Child: 1.8E-07 Teen: 4.6E-08 Adult: 2.3E-07	Child: 3.7E-05 Teen: 9.2E-06 Adult: 4.6E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Calcium Cancrinite	5.7E-04	Child: 1.1E-04 Teen: 2.8E-05 Adult: 1.4E-04	Child: 2.2E-02 Teen: 5.6E-03 Adult: 2.8E-02	Child: 6.1E-02 Teen: 1.5E-02 Adult: 7.7E-02	Child: 64% Teen: 64% Adult: 64%
Gallium Trioxide	4.0E-07	Child: 7.8E-08 Teen: 2.0E-08 Adult: 9.9E-08	Child: 1.6E-05 Teen: 3.9E-06 Adult: 2.0E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Hydrogarnet	1.4E-04	Child: 2.7E-05 Teen: 6.8E-06 Adult: 3.4E-05	Child: 5.4E-03 Teen: 1.4E-03 Adult: 6.9E-03	Child: 4.4E-02 Teen: 1.1E-02 Adult: 5.6E-02	Child: 88% Teen: 88% Adult: 88%
Perovskite	1.9E-04	Child: 3.8E-05 Teen: 9.4E-06 Adult: 4.8E-05	Child: 7.5E-03 Teen: 1.9E-03 Adult: 9.5E-03	Child: 4.7E-02 Teen: 1.2E-02 Adult: 5.9E-02	Child: 84% Teen: 84% Adult: 84%
Niobium Pentoxide	6.6E-07	Child: 1.3E-07 Teen: 3.2E-08 Adult: 1.6E-07	Child: 2.6E-05 Teen: 6.4E-06 Adult: 3.2E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Thorium Oxide	4.7E-07	Child: 9.2E-08 Teen: 2.3E-08 Adult: 1.2E-07	Child: 1.8E-05 Teen: 4.6E-06 Adult: 2.3E-05	Child: 3.9E-02 Teen: 9.8E-03 Adult: 4.9E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Salt Cake COPCs					
Sodium Oxalate	7.5E-04	Child: 1.5E-04 Teen: 3.7E-05 Adult:1.9E-04	Child: 1.5E-02 Teen: 3.7E-03 Adult: 1.9E-02	Child: 5.7E-02 Teen: 1.4E-02 Adult: 6.9E-02	Child: 71% Teen: 71% Adult: 72%
Aluminum Oxide	4.7E-04	Child: 9.2E-05 Teen: 2.3E-05 Adult: 1.2E-04	Child: 9.2E-03 Teen: 2.3E-03 Adult: 1.2E-02	Child: 4.8E-02 Teen: 1.2E-02 Adult: 6.1E-02	Child: 81% Teen: 81% Adult: 81%

Notes:
Target HQ = 0.2
HQs presented in **bold** if Target HQ is exceeded
HQ cumulative = HQ (baseline) + HQ (operational)
Due to rounding, HQs might appear slightly off

Table 7.4 presents the predicted health risks associated with exposures to identified COPCs for nearby residents for all life stages (i.e., infancy, toddler, child, teen, and adult). The results of the quantitative risk analysis indicate that there are no health concerns for nearby residents for all life stages (as indicated by the calculated HQs for identified COPCs) resulting from potential exposures to Project-related emissions.

Table 7.4 Predicted Health Risks Associated with Potential Exposure to Bauxite Residue and Salt Cake COPCs in PM_{10} (24-hr) for Nearby Residential Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Aluminum Goethite	9.8E-04	All resident life stages: 9.0E-04	All resident life stages: 9.0E-02	All resident life stages: 2.7E-01	All resident life stages: 67%
Hematite	8.8E-04	All resident life stages: 8.1E-04	All resident life stages: 1.6E-02	All resident life stages: 2.0E-01	All resident life stages: 92%
Anatase and Rutile	1.9E-04	All resident life stages: 1.8E-04	All resident life stages: 1.8E-02	All resident life stages: 2.0E-01	All resident life stages: 91%
Boehmite	1.0E-04	All resident life stages: 9.3E-05	All resident life stages: 9.3E-03	All resident life stages: 1.9E-01	All resident life stages: 95%
Zircon	1.4E-05	All resident life stages: 1.3E-05	All resident life stages: 2.6E-03	All resident life stages: 1.8E-01	All resident life stages: 99%
Gypsum	7.1E-06	All resident life stages: 6.5E-06	All resident life stages: 6.5E-04	All resident life stages: 1.8E-01	All resident life stages: 99.6%
Sodium Sulphate	3.3E-06	All resident life stages: 3.2E-06	All resident life stages: 6.5E-04	All resident life stages: 1.8E-01	All resident life stages: 99.6%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Sodium Fluoride	9.4E-07	All resident life stages: 8.7E-07	All resident life stages: 3.2E-05	All resident life stages: 1.8E-01	All resident life stages: 99.99%
Chromium Trioxide	9.4E-06	All resident life stages: 8.7E-06	All resident life stages: 6.7E-03	All resident life stages: 1.9E-01	All resident life stages: 96%
Vanadium Pentoxide	9.4E-06	All resident life stages: 8.7E-06	All resident life stages: 1.7E-02	All resident life stages: 2.0E-01	All resident life stages: 91%
Manganese Oxide	1.7E-06	All resident life stages: 1.5E-06	All resident life stages: 1.8E-03	All resident life stages: 1.8E-01	All resident life stages: 99%
Zinc Oxide	2.4E-07	All resident life stages: 2.2E-07	All resident life stages: 9.0E-05	All resident life stages: 1.8E-01	All resident life stages: 99.9%
Lead Oxide	3.3E-07	All resident life stages: 3.0E-07	All resident life stages: 2.0E-03	All resident life stages: 1.8E-01	All resident life stages: 99%
Yttrium Trioxide	4.5E-07	All resident life stages: 4.1E-07	All resident life stages: 4.1E-04	All resident life stages: 1.8E-01	All resident life stages: 99.8%
Copper Oxide	1.9E-07	All resident life stages: 1.7E-07	All resident life stages: 1.7E-04	All resident life stages: 1.8E-01	All resident life stages: 99.9%
Strontium Oxide	4.5E-07	All resident life stages: 4.1E-07	All resident life stages: 8.2E-05	All resident life stages: 1.8E-01	All resident life stages: 99.99%
Cerium Oxide	9.4E-07	All resident life stages: 8.7E-07	All resident life stages: 1.7E-04	All resident life stages: 1.8E-01	All resident life stages: 99.9%
Calcium Cancrinite	5.7E-04	All resident life stages: 5.3E-04	All resident life stages: 1.1E-01	All resident life stages: 2.9E-01	All resident life stages: 63%
Gallium Trioxide	4.0E-07	All resident life stages: 3.7E-07	All resident life stages: 7.4E-05	All resident life stages: 1.8E-01	All resident life stages: 99.99%
Hydrogarnet	1.4E-04	All resident life stages: 1.3E-04	All resident life stages: 2.6E-02	All resident life stages: 2.1E-01	All resident life stages: 88%
Perovskite	1.9E-04	All resident life stages: 1.8E-04	All resident life stages: 3.6E-02	All resident life stages: 2.2E-01	All resident life stages: 84%
Niobium Pentoxide	6.6E-07	All resident life stages: 6.1E-07	All resident life stages: 1.2E-04	All resident life stages: 1.8E-01	All resident life stages: 99.9%
Thorium Oxide	4.7E-07	All resident life stages: 4.3E-07	All resident life stages: 8.7E-05	All resident life stages: 1.8E-01	All resident life stages: 99.99%
Salt Cake COPCs					
Sodium Oxalate	7.5E-04	All resident life stages: 6.9E-04	All resident life stages: 6.9E-02	All resident life stages: 2.7E-01	All resident life stages: 74%
Aluminum Oxide	4.7E-04	All resident life stages: 4.3E-04	All resident life stages: 4.3E-02	All resident life stages: 2.2E-01	All resident life stages: 81%

Notes:
Target HQ = 1
HQs presented in **bold** if Target HQ is exceeded
HQ cumulative = HQ (baseline) + HQ (operational)

"All resident life stages" represents each of the individual life stages, separately (i.e., infant, toddler, child, teen, and adult life stages)
Due to rounding, HQs might appear slightly off

Table 7.5 presents the predicted health risks associated with exposures to identified COPCs for students and teachers at the primary school. The results of the quantitative risk analysis indicate that there are no health concerns for students and teachers (as indicated by the calculated HQs for identified COPCs). It is noted that the summed HQ resulting from potential exposures to Project plus Background contributions to ambient concentrations is primarily attributable to exposures to background contributions and drives over 45% to as high as 99% of the predicted health risks.

Table 7.5 Predicted Health Risks Associated with Potential Exposure to Bauxite Residue and Salt Cake COPCs in $PM_{2.5}$ (24-hr) for School Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Aluminum Goethite	2.8E-03	Child: 5.4E-04 Teen: 1.3E-04 Adult: 6.8E-04	Child: 5.4E-02 Teen: 1.3E-02 Adult: 6.8E-02	Child: 1.1E-01 Teen: 2.7E-02 Adult: 1.3E-01	Child: 46% Teen: 48% Adult: 49%
Hematite	2.5E-03	Child: 4.8E-04 Teen: 1.2E-04 Adult: 6.1E-04	Child: 9.7E-03 Teen: 2.4E-03 Adult: 1.2E-02	Child: 6.1E-02 Teen: 1.5E-02 Adult: 7.6E-02	Child: 84% Teen: 84% Adult: 84%
Anatase and Rutile	5.4E-04	Child: 1.1E-04 Teen: 2.6E-05 Adult: 1.3E-04	Child: 1.1E-02 Teen: 2.6E-03 Adult: 1.3E-02	Child: 6.2E-02 Teen: 1.6E-02 Adult: 7.7E-02	Child: 83% Teen: 83% Adult: 83%
Boehmite	2.8E-04	Child: 5.5E-05 Teen: 1.4E-05 Adult: 7.0E-05	Child: 5.5E-03 Teen: 1.4E-03 Adult: 7.0E-03	Child: 5.7E-02 Teen: 1.4E-02 Adult: 7.1E-02	Child: 90% Teen: 90% Adult: 90%
Zircon	4.0E-05	Child: 7.7E-06 Teen: 1.9E-06 Adult: 9.8E-06	Child: 1.5E-03 Teen: 3.9E-04 Adult: 2.0E-03	Child: 5.3E-02 Teen: 1.3E-02 Adult: 6.6E-02	Child: 97% Teen: 97% Adult: 97%
Gypsum	2.0E-05	Child: 3.9E-06 Teen: 9.7E-07 Adult: 4.9E-06	Child: 3.9E-04 Teen: 9.7E-05 Adult: 4.9E-04	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99% Teen: 99% Adult: 99%
Sodium Sulphate	9.9E-06	Child: 1.9E-06 Teen: 4.8E-07 Adult: 2.4E-06	Child: 3.9E-04 Teen: 9.7E-05 Adult: 4.9E-04	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99% Teen: 99% Adult: 99%
Sodium Fluoride	2.6E-06	Child: 5.2E-07 Teen: 1.3E-07 Adult: 6.5E-07	Child: 1.9E-05 Teen: 4.8E-06 Adult: 2.4E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.99% Teen: 99.99% Adult: 99.99%
Chromium Trioxide	2.6E-05	Child: 5.2E-06 Teen: 1.3E-06 Adult: 6.5E-06	Child: 4.0E-03 Teen: 9.9E-04 Adult: 5.0E-03	Child: 5.5E-02 Teen: 1.4E-02 Adult: 6.9E-02	Child: 93% Teen: 93% Adult: 93%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Vanadium Pentoxide	2.6E-05	Child: 5.2E-06 Teen: 1.3E-06 Adult: 6.5E-06	Child: 1.0E-02 Teen: 2.6E-03 Adult: 1.3E-02	Child: 6.1E-02 Teen: 1.6E-02 Adult: 7.7E-02	Child: 83% Teen: 84% Adult: 83%
Manganese Oxide	4.6E-06	Child: 9.0E-07 Teen: 2.3E-07 Adult: 1.1E-06	Child: 1.1E-03 Teen: 2.7E-04 Adult: 1.4E-03	Child: 5.2E-02 Teen: 1.3E-02 Adult: 6.5E-02	Child: 98% Teen: 98% Adult: 98%
Zinc Oxide	6.6E-07	Child: 1.3E-07 Teen: 3.2E-08 Adult: 1.6E-07	Child: 5.4E-05 Teen: 1.3E-05 Adult: 6.8E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Lead Oxide	9.2E-07	Child: 1.8E-07 Teen: 4.5E-08 Adult: 2.3E-07	Child: 1.2E-03 Teen: 3.0E-04 Adult: 1.5E-03	Child: 5.2E-02 Teen: 1.3E-02 Adult: 6.6E-02	Child: 98% Teen: 98% Adult: 98%
Yttrium Trioxide	1.3E-06	Child: 2.4E-07 Teen: 6.1E-08 Adult: 3.1E-07	Child: 2.4E-04 Teen: 6.1E-05 Adult: 3.1E-04	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.5% Teen: 99.5% Adult: 99.5%
Copper Oxide	5.3E-07	Child: 1.0E-07 Teen: 2.6E-08 Adult: 1.3E-07	Child: 1.0E-04 Teen: 2.6E-05 Adult: 1.3E-04	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.8% Teen: 99.8% Adult: 99.8%
Strontium Oxide	1.3E-06	Child: 2.4E-07 Teen: 6.1E-08 Adult: 3.1E-07	Child: 4.9E-05 Teen: 1.2E-05 Adult: 6.2E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Cerium Oxide	2.6E-06	Child: 5.2E-07 Teen: 1.3E-07 Adult: 6.5E-07	Child: 1.0E-04 Teen: 2.6E-05 Adult: 1.3E-04	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.8% Teen: 99.8% Adult: 99.8%
Calcium Cancirnite	1.6E-03	Child: 3.1E-04 Teen: 7.8E-05 Adult: 3.9E-04	Child: 6.2E-02 Teen: 1.6E-02 Adult: 7.9E-02	Child: 1.1E-01 Teen: 2.9E-02 Adult: 1.4E-01	Child: 45% Teen: 45% Adult: 45%
Gallium Trioxide	1.1E-06	Child: 2.2E-07 Teen: 5.5E-08 Adult: 2.8E-07	Child: 4.4E-05 Teen: 1.1E-05 Adult: 5.5E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Hydrogarnet	3.9E-04	Child: 7.6E-05 Teen: 1.9E-05 Adult: 9.6E-05	Child: 1.5E-02 Teen: 3.8E-03 Adult: 1.9E-02	Child: 6.6E-02 Teen: 1.7E-02 Adult: 8.3E-02	Child: 77% Teen: 77% Adult: 77%
Perovskite	5.4E-04	Child: 1.1E-04 Teen: 2.6E-05 Adult: 1.3E-04	Child: 2.1E-02 Teen: 5.3E-03 Adult: 2.7E-02	Child: 7.2E-02 Teen: 1.8E-02 Adult: 9.1E-02	Child: 71% Teen: 71% Adult: 71%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Niobium Pentoxide	1.9E-06	Child: 3.6E-07 Teen: 9.0E-08 Adult: 4.6E-07	Child: 7.2E-05 Teen: 1.8E-05 Adult: 9.1E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Thorium Oxide	1.3E-06	Child: 2.6E-07 Teen: 6.4E-08 Adult: 3.3E-07	Child: 5.2E-05 Teen: 1.3E-05 Adult: 6.5E-05	Child: 5.1E-02 Teen: 1.3E-02 Adult: 6.4E-02	Child: 99.9% Teen: 99.9% Adult: 99.9%
Salt Cake COPCs					
Sodium Oxalate	2.1E-03	Child: 4.1E-04 Teen: 1.0E-04 Adult: 5.2E-04	Child: 4.1E-02 Teen: 1.0E-02 Adult: 5.2E-02	Child: 9.1E-02 Teen: 2.0E-02 Adult: 1.1E-01	Child:55% Teen: 50% Adult: 55%
Aluminum Oxide	1.3E-03	Child: 2.6E-04 Teen: 6.4E-05 Adult: 3.3E-04	Child: 2.6E-02 Teen: 6.4E-03 Adult: 3.3E-02	Child: 7.7E-02 Teen: 1.9E-02 Adult: 9.7E-02	Child: 66% Teen: 67% Adult: 66%

Notes:
Target HQ = 0.2
HQs presented in **bold** if Target HQ is exceeded
HQ cumulative = HQ (baseline) + HQ (operational)
Due to rounding, HQs might appear slightly off

Table 7.6 presents the predicted health risks associated with exposures to identified COPCs by nearby residents for all life stages (i.e., infancy, toddler, child, teen, and adult). The results of the quantitative risk analysis indicate that there are no health concerns for nearby residents for all life stages (as indicated by the calculated HQs for identified COPCs) resulting from potential exposures to Project-related emissions.

Table 7.6 Predicted Health Risks Associated with Potential Exposure to Bauxite Residue and Salt Cake COPCs in $PM_{2.5}$ (24-hr) for Nearby Residential Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Aluminum Goethite	2.8E-03	All resident life stages: 2.5E-03	All resident life stages: 2.5E-01	All resident life stages: 4.9E-01	All resident life stages: 49%
Hematite	2.5E-03	All resident life stages: 2.3E-03	All resident life stages: 4.6E-02	All resident life stages: 2.9E-01	All resident life stages: 84%
Anatase and Rutile	5.4E-04	All resident life stages: 5.0E-04	All resident life stages: 5.0E-02	All resident life stages: 2.9E-01	All resident life stages: 83%
Boehmite	2.8E-04	All resident life stages: 2.6E-04	All resident life stages: 2.6E-02	All resident life stages: 2.7E-01	All resident life stages: 90%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m³)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m³)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Zircon	4.0E-05	All resident life stages: 3.6E-05	All resident life stages: 7.3E-03	All resident life stages: 2.5E-01	All resident life stages: 97%
Gypsum	2.0E-05	All resident life stages: 1.8E-05	All resident life stages: 1.8E-03	All resident life stages: 2.4E-01	All resident life stages: 99%
Sodium Sulphate	9.9E-06	All resident life stages: 9.1E-06	All resident life stages: 1.8E-03	All resident life stages: 2.4E-01	All resident life stages: 99%
Sodium Fluoride	2.6E-06	All resident life stages: 2.4E-06	All resident life stages: 9.0E-05	All resident life stages: 2.4E-01	All resident life stages: 99.99%
Chromium Trioxide	2.6E-05	All resident life stages: 2.4E-05	All resident life stages: 1.9E-02	All resident life stages: 2.6E-01	All resident life stages: 93%
Vanadium Pentoxide	2.6E-05	All resident life stages: 2.4E-05	All resident life stages: 4.9E-02	All resident life stages: 2.9E-01	All resident life stages: 83%
Manganese Oxide	4.6E-06	All resident life stages: 4.3E-06	All resident life stages: 5.1E-03	All resident life stages: 2.5E-01	All resident life stages: 98%
Zinc Oxide	6.6E-07	All resident life stages: 6.1E-07	All resident life stages: 2.5E-04	All resident life stages: 2.4E-01	All resident life stages: 99.9%
Lead Oxide	9.2E-07	All resident life stages: 8.5E-07	All resident life stages: 5.7E-03	All resident life stages: 2.5E-01	All resident life stages: 98%
Yttrium Trioxide	1.3E-06	All resident life stages: 1.2E-06	All resident life stages: 1.2E-03	All resident life stages: 2.4E-01	All resident life stages: 99.5%
Copper Oxide	5.3E-07	All resident life stages: 4.9E-07	All resident life stages: 4.9E-04	All resident life stages: 2.4E-01	All resident life stages: 99.8%
Strontium Oxide	1.3E-06	All resident life stages: 1.2E-06	All resident life stages: 2.3E-04	All resident life stages: 2.4E-01	All resident life stages: 99.9%
Cerium Oxide	2.6E-06	All resident life stages: 2.4E-06	All resident life stages: 4.9E-04	All resident life stages: 2.4E-01	All resident life stages: 99.8%
Calcium Cancrinite	1.6E-03	All resident life stages: 1.5E-03	All resident life stages: 2.9E-01	All resident life stages: 5.3E-01	All resident life stages: 45%
Gallium Trioxide	1.1E-06	All resident life stages: 1.0E-06	All resident life stages: 2.1E-04	All resident life stages: 2.4E-01	All resident life stages: 99.9%
Hydrogarnet	3.9E-04	All resident life stages: 3.6E-04	All resident life stages: 7.2E-02	All resident life stages: 3.1E-01	All resident life stages: 77%
Perovskite	5.4E-04	All resident life stages: 5.0E-04	All resident life stages: 9.9E-02	All resident life stages: 3.4E-01	All resident life stages: 71%
Niobium Pentoxide	1.9E-06	All resident life stages: 1.7E-06	All resident life stages: 3.4E-04	All resident life stages: 2.4E-01	All resident life stages: 99.9%

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	HQ (OPERATIONAL)	HQ (CUMULATIVE)	% HQ ATTRIBUTABLE TO BACKGROUND
Thorium Oxide	1.3E-06	All resident life stages: 1.2E-06	All resident life stages: 2.4E-04	All resident life stages: 2.4E-01	All resident life stages: 99.9%
Salt Cake COPCs					
Sodium Oxalate	2.1E-03	All resident life stages: 1.9E-03	All resident life stages: 1.9E-01	All resident life stages: 3.9E-01	All resident life stages: 51%
Aluminum Oxide	1.3E-03	All resident life stages: 1.2E-03	All resident life stages: 1.2E-01	All resident life stages: 3.6E-01	All resident life stages: 66%

Notes:
Target HQ = 1
HQs presented in **bold** if Target HQ is exceeded
HQ cumulative = HQ (baseline) + HQ (operational)
"All resident life stages" represents each of the individual life stages, separately (i.e., infant, toddler, child, teen, and adult life stages)

7.1.1.2 *RESULTS OF THE CARCINOGENIC ASSESSMENT*

Two carcinogenic COPCs are assessed in this HHA: chromium trioxide and arsenic trioxide. For the above noted COPCs, the health-based exposure limits represent an ambient air concentration that corresponds to *a de minimis* risk level of 1 per 100,000 excess cancer risk.

Tables 7.7 and 7.8 summarize the predicted health risks associated with carcinogenic COPCs in PM_{10} for students and teachers at the primary school as well as nearby residents.

For potential inhalation exposures of chromium trioxide, arsenic trioxide and PM_{10} from Project-related emissions, the incremental lifetime cancer risks range from 0.000037 to 0.45 per 100,1000 for all human receptors.

This increase would be undetectable using available epidemiological data and statistics, particularly in smaller populations that may reside near the Project.

The risk analysis indicates *de minimis* incremental risk of cancer associated with exposures to identified COPCs for students and teachers at the primary school as well as nearby residents.

Table 7.7 Predicted Health Risks Associated with Potential Exposure to Carcinogenic COPCs in PM_{10} (Annual) for School Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	INCREASED LIFETIME CANCER RISK (OPERATIONAL)
Chromium Trioxide	2.8E-06	Child: 4.9E-08 Teen: 1.4E-08 Adult: 5.1E-07	Child: 1.1E-02 Teen: 3.3E-03 Adult: 1.2E-01
Arsenic Trioxide	1.4E-07	Child: 2.5E-09 Teen: 7.0E-10 Adult: 2.6E-08	Child: 3.7E-05 Teen: 1.1E-05 Adult: 3.8E-04

Table 7.8 Predicted Health Risks Associated with Potential Exposures to Carcinogenic COPCs in PM_{10} (Annual) for Nearby Residential Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	INCREASED LIFETIME CANCER RISK (OPERATIONAL)
Chromium Trioxide	2.8E-06	Infant: 1.7E-08 Toddler: 1.5E-07 Child: 2.3E-07 Teen: 2.6E-07 Adult: 1.9E-06	Infant: 3.8E-03 Toddler: 3.5E-02 Child: 5.4E-02 Teen: 6.2E-02 Adult: 4.5E-01
Arsenic Trioxide	1.4E-07	Infant: 8.3E-10 Toddler: 7.4E-09 Child: 1.2E-08 Teen: 1.3E-08 Adult: 9.6E-08	Infant: 1.2E-05 Toddler: 1.1E-04 Child: 1.7E-04 Teen: 2.0E-04 Adult: 1.4E-03

Table 7.9 and

Table 7.10 summarize the predicted health risks associated with carcinogenic COPCs in $PM_{2.5}$ for students and teachers at the primary school as well as nearby residents.

For potential inhalation exposures of chromium trioxide, arsenic trioxide and $PM_{2.5}$ from Project-related emissions, the incremental lifetime cancer risks range from 0.0000034 to 0.19 per 100,1000 for all human receptors.

This increase would be undetectable using available epidemiological data and statistics, particularly in smaller populations that may reside near the Project.

The risk analysis indicates *de minimis* incremental risk of cancer associated with exposures to identified COPCs for students and teachers at the primary school as well as nearby residents.

Table 7.9 Predicted Health Risks Associated with Potential Exposure to Carcinogenic COPCs in $PM_{2.5}$ (Annual) for School Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (MG/M3)	ADJUSTED OPERATIONAL CONTRIBUTION (MG/M3)	INCREASED LIFETIME CANCER RISK (OPERATIONAL)
Chromium Trioxide	9.0E-07	Child: 1.6E-08 Teen: 4.5E-09 Adult: 1.7E-07	Child: 3.7E-03 Teen: 1.1E-03 Adult: 3.8E-02
Arsenic Trioxide	4.5E-08	Child: 7.9E-10 Teen: 2.3E-10 Adult: 8.3E-09	Child: 1.2E-05 Teen: 3.4E-06 Adult: 1.2E-04

Table 7.10 Predicted Health Risks Associated with Potential Exposure to Carcinogenic COPCs in $PM_{2.5}$ (Annual) for Nearby Residential Receptors

BAUXITE RESIDUE COPCS	OPERATIONAL CONTRIBUTION (mg/m^3)	ADJUSTED OPERATIONAL CONTRIBUTION (mg/m^3)	INCREASED LIFETIME CANCER RISK (OPERATIONAL)
Chromium Trioxide	9.0E-07	Infant: 5.3E-09 Toddler: 4.8E-08 Child: 7.4E-08 Teen: 8.5E-08 Adult: 6.2E-07	Infant: 1.2E-03 Toddler: 1.1E-02 Child: 1.7E-02 Teen: 2.0E-02 Adult: 1.4E-01
Arsenic Trioxide	4.5E-08	Infant: 2.7E-10 Toddler: 2.4E-09 Child: 3.7E-09 Teen: 4.3E-09 Adult: 3.1E-08	Infant: 4.0E-06 Toddler: 3.6E-05 Child: 5.6E-05 Teen: 6.3E-05 Adult: 4.6E-04

7.2 UNCERTAINTY ANALYSIS

Conducting a risk assessment involves many steps within the process and assumptions are made at each stage to account for the lack of scientific data pertaining to the given project. Due to the application of these assumptions, uncertainty is inherently involved in the process. However, as discussed above in **Sections 4.5, 5.5,** and **6.4,** these assumptions are conservative and result in an overestimation of the true risk.

The following sources of uncertainty in the HHA are noted:

- The use of conservative modelled data to predict future project-related emissions.
    - The air dispersion model used to calculate predicted PM10 and PM2.5 ambient ground level concentrations generated by the AAL facility only (i.e., Project contribution) also identified the concentrations at the worst-case off-site locations. These worst-case concentrations were selected to develop the COPC-specific exposure concentrations used for the purpose of the exposure assessment. Although the nearest off-site receptor is located approximately 1.9 km west of the AAL facility, it was conservatively assumed that all identified receptors were exposed to the worst-case concentrations found at the Facility boundary and that no level of air quality

attenuation occurred between the AAL facility boundary and any of the identified receptors. Use of these worst-case concentrations is considered a conservative approach and is likely to overestimate risk.

- Additionally, the air dispersion model evaluated five (5) distinct scenarios, with each scenario representing a stage of the BRDA elevation construction. Predicted air concentrations used for the purpose of the HHA were obtained from scenarios with the highest predicted concentrations (i.e., scenarios 1 and 2). It should be noted that scenarios 1 and 2 are transient and represent the earliest stages of the BRDA elevation construction process, whereas scenario 5 represents the final stage and completion of the BRDA elevation. Given that in this final stage, the surface area of the BRDA would be significantly reduced, predicted air concentrations are the lowest in scenario 5. Therefore, using predicted air concentrations from "worst-case" scenarios 1 and 2 for the purpose of the HHA is considered a conservative approach, and is likely to overestimate risk.

- Calculating exposure concentrations for constituents of bauxite residue and salt cake constituents.
  - No site-specific information is available as to how much of the particulate matter generated by the AAL Facility would consist of bauxite residue and/or salt cake. As such, to calculate COPC-specific exposure concentrations, it was conservatively assumed that all particulate matter generated would consist entirely of both bauxite residue and salt cake constituents, concurrently. Therefore, this approach is likely to overestimate predicted health risks.
  - The propensity of bauxite residue and salt cake to be suspended as dusts is also likely overestimated given the moisture content of both bauxite residue (21%) and salt cake (41% to 46%, with a mean of 44%) is high. It should be noted that given the high moisture content found in salt cake (typically around 44% in weight), it is likely that dispersion of salt cake constituents into the atmosphere as particulate matter would be limited, if not negligible. Therefore, this evaluation method is likely to overestimate risk.
- The use of conservative exposure assumptions to estimate exposures by human receptors.
  - Conservative assumptions were applied when calculating exposure estimates (i.e., assumptions for number of hours and days of exposures) for all identified receptors. Students attending the primary school were conservatively assumed to spend 9 hours/day and 38 weeks/year at school to account for regular attendance at before- and after-school programs as well as summer programs. Although the school provides education at the primary level, children up to age 13 were evaluated to conservatively capture those students that may be older. Applying these conservative exposure assumptions is likely to overestimate risk; however, despite this conservative approach, there were no predicted risk identified for students at the primary school.
- Human exposure to background particulates remains the major source of predicted health risks.
  - In examining the data collected from measured regional background concentrations as well as predicted (Project-only) air concentrations for PM_{10} and $PM_{2.5}$, it is evident that background particulate matter constitutes a significant fraction of the total or cumulative predicted ambient concentrations (i.e., background + Project contribution) dispersed into the Project Study Area. For PM_{10} and $PM_{2.5}$ (annual and 24-hr), background concentrations range between 35% to 94% of total predicted ambient concentrations and make up over 50% in most cases. Given the significance of regional background particulate concentrations in the Study Area relative to predicted Project-emissions, background PM remains the major source of predicted health risks.

The risks identified in **Sections 7.1 and 7.2** are therefore, considered theoretical (i.e., there is the potential for risk, but there is some uncertainty as to whether adverse effects would be evident in the human receptors when exposed to the predicted concentrations).

8 SUMMARY AND CONCLUSIONS

Aughinish Alumina Limited (AAL) retained WSP Canada Inc. (WSP), in collaboration with Golder Associates Ireland Ltd. (Golder), to complete this Human Health Assessment (HHA) to support the Environmental Impact Assessment for the proposed expansion of the Bauxite Residue Disposal Area (BRDA) and the Salt Cake Disposal Cell (SCDC). AAL operates a long-established alumina plant, located on Aughinish Island on the southern side of the Shannon Estuary near the village of Foynes, County of Limerick. The landholding extends to c. 601 hectares and is located c. 6 km north-west of Askeaton and c. 30 km west of Limerick City Centre.

Bauxite residue, a by-product of the alumina production process, is deposited within the BRDA located to the south-west of the plant. The BRDA covers an area of approximately 184 hectares (ha). The SCDC, located within the BRDA, is an engineered cell that stores the salt cake hazardous waste created from removing the organic impurities when the bauxite is dissolved. The Project site plan is shown on **Figure 1.1.**

The proposed development consists of works to the BRDA comprising of an expansion to increase its disposal capacity to accommodate additional bauxite residue arising from the continued operation of the permitted alumina plant located on the wider AAL facility. The proposed increase in disposal capacity to the BRDA will result in a proposed increase in height of c.12m above the currently permitted stage 10 level (c. 32m OD) to a final stage 16 level (c. 44m OD). No increase to the existing footprint of the BRDA is proposed.

The proposed method of raising the BRDA will be the upstream method, consistent with the construction methodology for the current BRDA and involves the construction of rock fill embankments (Stages), offset internationally, and founded on the previously deposited and farmed bauxite residue, in 2 m high vertical lifts. The overall stack is raised systematically as the stages are filled with bauxite residue, farmed, carbonated, and compacted, prior to deposition of the next layer.

To complete the HHA, WSP evaluated the toxicity of bauxite residue and salt cake by-products, assessed the source-pathway-receptor linkage to understand causal relationship between predicted exposures and bauxite residues, as well as characterized health risks, if any, of nearby human populations with potential exposures released from the Project.

Given that bauxite residues and salt cake waste by-products are mixtures and due to their limited (or absent) toxicology data, a literature search and review was completed for their constituents to determine the toxicology and associated health effects from exposures to solid waste mixtures as well as identify which chemicals of potential concern (or COPCs) will be carried forward for further evaluation in the HHA. All constituents were identified as COPCs for further assessment in the HHA, with exception of those constituents that were listed as “Generally Recognized as Safe” (“GRAS”) by the US Food and Drug Administration (FDA).

Those substances listed as GRAS have been concluded to have “***no evidence in the available information …that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future***” (US FDA, 2018). I

It was determined that constituents of bauxite residue and salt cake that would be screened out from further assessment included: moisture, Bayer sodalite, Gibbsite, Quartz, Sodium carbonate (baking soda), Carbonate apatite, Sodium bicarbonate (baking soda), Sodium aluminate, Sodium hydroxide, Magnesium oxide, and potassium carbonate. The constituents of bauxite residue and salt cake that were screened out from further evaluation in the HHA totaled 33.5% and 61.5% of the total weight percentage, respectively. **Table 4.1** and **Table 4.2** summarize the compositions of bauxite residue and salt cake, as well as indicate which constituents were carried forward as COPCs.

Before assessing the potential health effects of Project-related emissions, the HHA characterized existing community health (i.e., Limerick County) by referring to several credible health-related sources including a 2015 Health Profile for the City of Limerick, a 2019 Health in Ireland report, and key health statistics from Ireland Central Statistics Office. Collectively, these sources suggested that the death rate for many diseases in Limerick is lower or equivalent to other counties and the national average. Death rates were only marginally higher for diseases such as myocardial infraction and other diseases of the circulatory system, and two times higher for diseases of the

blood, blood forming organs, and immunological disorders. However, it is important to note that data between 2009 to 2017 indicates that death rates for these diseases (and many others) are on a steady decline in Limerick.

The human receptors evaluated in the HHA were identified based on land use(s) within the Project Study Area and included sensitive subpopulations such as children and residents. The following human receptors were considered and evaluated in the HHA:

— Young children and teen students in a primary school (Scoil Naisiunta Sheanain);
— Adult workers (e.g., teachers) at the primary school; and,
— Individuals who live in residential communities near the Project.

A toxicological and jurisdictional review of available ambient air exposure limits was completed for all identified COPCs. Health-based TRVs were selected for each COPC and averaging period, if available, based on information obtained during this review.

For non-cancer health endpoints, the findings of the risk analysis concluded the following:

- There are no health concerns associated with exposures to Project-related COPCs for students and teachers at the nearby primary school.

- Predicted health risks for students and teachers at the nearby primary school are associated with exposures to background ambient concentrations of PM_{10} and $PM_{2.5}$; constituting over 45% to as high as 99% of the predicted health risks.

- There are no health concerns associated with exposures to Project-related COPCs for nearby residents, for all life stages (i.e., infancy, toddler, child, teen, and adult).

For cancer health endpoints, the findings of the risk analysis concluded the following:

- Potential inhalation exposures of chromium trioxide, arsenic trioxide and PM_{10} from Project-related emissions are associated with *de minimis* incremental risk of cancer for students and teachers at the primary school as well as nearby residents.

The HHA was carried out to err on the side of caution to ensure that the results are protective of human health. As such, it is important to highlight that and that the conclusions were based on the following conservative approach that have been applied in the HHA:

- The risk analysis applied worst-case Project emissions of PM_{10} and $PM_{2.5}$ at the Project boundary. That is, all human receptors evaluated in the HHA were assumed to be exposed to maximum 24-hr concentrations, calculated as 90^{th} percentile concentrations, at the Project boundary. In addition, the exposure assessment only considered predicted air concentrations from scenario 1, which represents the earliest stage of BRDA elevation construction and the worst-case predicted air concentrations. Predicted air concentrations show a slight decrease as the BRDA is raised (i.e., with each successive scenario), with the final scenario (5) having the lowest predicted air concentrations as the surface area of the BRDA is significantly reduced compared to the other scenarios. Therefore, using predicted air concentrations from scenario 1 in addition to assuming that human receptors are present at the Project boundary exposed to maximum concentrations for the purpose of the exposure assessment is considered an overly conservative approach, and is likely to overestimate risk.
- These worst-case concentrations were selected to develop the COPC-specific exposure concentrations used for the purpose of the exposure assessment. Given that these concentrations are based along the AAL facility boundary, and that the nearest off-site receptor is located approximately 1.9 kilometres to the west of the AAL facility, use of these worst-case concentrations is considered a conservative approach, and is likely to overestimate risk.
- The HHA assumed that emissions of the bauxite residue and salt cake predominantly occurs as particulates or fugitive dusts. To assess potential exposures to bauxite residue and salt cake, this HHA assumed their constituents will be present in the dusts emitted from the Project at the same percentage composition. That

is, the predicted concentration for each COPC is based on the percentage of each COPC modelled PM_{10} (annual and 24-hr) and $PM_{2.5}$ (annual and 24-hr) concentrations to reflect the percentage of each COPC in the dust. Therefore, this HHA assumes that both bauxite residue and salt cake are both present as dust, with levels of their constituents present at the same percentage composition as in the solid waste by-product. This assumption maintains an overly conservative approach given that the moisture content of both bauxite residue (21%) and salt cake (41% to 46%, with a mean of 44%) are high. The presence of salt cake constituents as particulates or dust is highly unlikely given that moisture content is approximately 50%.

- Conservative assumptions were applied when calculating the exposure estimates (i.e., conservative assumptions for exposure durations and frequencies). For example, residents were assumed to be exposed to predicted exposure concentrations at the Project boundary continuously, for 24-hours, daily.
- Based on the findings of this HHA based on the use of maximum predicted exposure concentrations of PM_{10} and $PM_{2.5}$, and in combination with the use of overly conservative exposure assumptions applied in the risk analysis, bauxite residue and salt cake do not pose a health concern to human receptors in the nearby primary school and nearby residences.

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APPENDIX

A FINDINGS OF THE LITERATURE SEARCH AND REVIEW RELATED TO BAUXITE RESIDUE, TOXICOLOGY AND HEALTH EFFECTS

LEAD AUTHOR	TITLE	DATE	ABSTRACT	SUMMARY OF PERTINENT POINTS	COPCs	EXPOSURE PATHWAYS	TOXICITY	Other Comments/Figures
REVIEWS ON BAUXITE RESIDUE WASTE MANAGEMENT								
	Applications of bauxite residue A mini-review	2017	Bauxite residue is the waste generated during alumina production by Bayer s process. The amount of bauxite residue (40–50 wt%) generated depends on the quality of bauxite ore used for the processing. High alkalinity and high caustic content in bauxite residue causes environmental risk for fertile soil and ground water contamination. The caustic (NaOH) content in bauxite residue leads to human health risks, like dermal problems and irritation to eyes. Moreover, disposal of bauxite residue requires a large area; such problems can only be minimised by utilising bauxite residue effectively. For two decades, bauxite residue has been used as a binder in cement industries and filler/reinforcement for composite materials in the automobile industry. Valuable metals and oxides, like alumina (Al2O3), titanium oxide (TiO2) and iron oxide Fe2O3, were extracted from bauxite residue to reduce waste. Bauxite residue was utilised in construction and structure industries to make geopolymers. It was also used in the making of glass-ceramics and a coating material. Recently bauxite residue has been utilised to extract rare earth elements like scandium (Sc), yttrium (Y), lanthanum (La), cerium (Ce), neodymium (Nd) and dysprosium (Dy). In this review article, the mineralogical characteristics of bauxite residue are summarised and current progresses on utilisation of bauxite residue in different fields of science and engineering are presented in detail.	This review focuses on the **waste management and potential science and engineering applications** of bauxite residue (BR). The following noteworthy information has been summarized - Bauxite is the parent of lateric rocks, which consist of aluminum hydroxide minerals such as boehmite, diaspore, and gibbsite. - The initial uses of bauxite ore were for extraction of alumina through a two-step Bayer's process. - The residue left behind after the extraction of alumina is identified as the caustic insoluble waste known as BR. - The chemical composition of BR contains **alumina (Al2O3), iron oxide (FE2O3), silicon dioxide (SIO2), titanium dioxide (TIO2) and sodium oxide (NA2O) as major constituents**, and arsenic, chromium, copper, manganese, lead, zinc, etc., as minor constituents. - The environmental impacts of BR disposal are due to high alkalinity, presence of radionuclides, and toxic elements; therefore, sustainable disposal methods are required. -Current disposal methods of BR include **disposal of BR in lake/sea; disposal of BR as dry mud; BR drying in sun; disposal of BR as drained slurry; disposal of BR as conventional slurry**. - BR is effectively used in a wide variety of applications, including **improving soil fertility, production of construction related products such as bricks and cement, colouring agent in paints, as a catalyst for industrial applications, development of polymer and matrix composites, and development of geopolymers.** - As BR consists of toxic elements (as mentioned above), it is necessary to adsorb these elements from BR. BR also contains rare earth elements like scandium, yttrium, lanthanum, cerium, neodymium, and dysprosium; research is focusing on how to effectively extract these elements. - Utilization of BR can provide environmental and economic benefits, and can results in less groundwater and soil contamination. **Table 2. Major constituents of BR generated worldwide.** Major constituents (wt%) Country / References / Plant / Location / Fe_2O_3 / Al_2O_3 / SiO_2 / TiO_2 / Na_2O / CaO Australia / Wehr et al., 2006 / Bayne Smelters / Gladstone / 23–36 / 20–30 / 13–17 / 4–8 / 5–11 / 1–3 Rio Tinto / Gove / 30 / 20.8 / 17.1 / 8.3 / 8.1 / 2 ALCOA / Kwinana / 27–31 / 12–20 / 27–34 / 1–3 / 1–3.3 / 0–3 Brazil / Snars and Gilkes, 2009 / Alunorte / Barcarena / 45.6 / 15.1 / 15.6 / 4.29 / 7.5 / 1.16 Bosnia / Cablik, 2007 / Zvornik / Birac / 48.5 / 14.14 / 11.53 / 5.42 / 7.5 / – Canada / Vachon et al., 1994 / Rio Tinto / Vaudreuil / 31.60 / 20.61 / 8.89 / 6.23 / 10.26 / 1.66 China / Zhang et al., 2001 / Vimetco / Linzhou and Gongyi / 6–7 / 7–8 / 12–14 / 2–3 / 3–3.3 / – France / Pera et al., 1997 / Pechiney / Gardanne / 42 / 14 / 5 / 11 / 2 / – Germany / Mohapatra et al., 2000 / FRG Baudart / 38.75 / 20 / 13 / 5.5 / 8.16 / – Greece / Aluminium of Greece / Brenzila / 48 / 15.85 / 6.96 / 7.06 / 3.26 / – Hungary / MAL / Ajka / 38.75 / 15.2 / 10.15 / 4.6 / 8.12 / – India / Balco / Korba / 35–37 / 18–21 / 6–6.5 / 17–19 / 5–5.5 / 1.5–2 Hindalco / Renukoot / 25–36 / 17–19 / 7–8.5 / 14–16 / 5–6 / 3–4.5 Belgaum / 44–47 / 17–20 / 7–8.5 / 8–10 / 3–5 / 1–2 Malco / Mettur dam / 40–26 / 18–22 / 12–16 / 2–3 / 4–4.5 / 1–2.5 Nalco / Damanjodi / 48–53 / 17–19 / 5–6 / 3–4 / 4–4.6 / 0.8–1 Ireland / Xenidis et al., 2005 / RUSAL / Askeaton / 47 / 17 / 9 / 12 / 9 / – Italy / Sglavo et al., 2000 / Eurallumina SpA / Sardinia / 10 / 26 / 20 / 4 / 12 / 4.7 Jamaica / Mohapatra et al., 2000 / ALPART / Nain, St. Elizabeth / 50.9 / 14.2 / 3.4 / 6.87 / 3.18 / – Suriname / ALCOA / Paranam / 24.81 / 19 / 11.9 / 12.15 / 9.2 / – Spain / Snars and Gilkes, 2009 / Alcoa / Guinea / 37.5 / 21.2 / 4.4 / 11.43 / 3.6 / 5.51 Tiwan / Mohapatra et al., 2000 / Sigma Group / Kaohsiung / 41.3 / 20.21 / 17.93 / 2.9 / 3.8 / – Turkey / Et Aliminyum / Seydesehir / 37.84 / 20.24 / 15.27 / 6.15 / 9.43 / 2.23 USA / Alcoa / Arkansas / 55.6 / 12.15 / 4.5 / 4.5 / 2–5 / – UK / Srikanth et al., 2009 / Alcan / Lynemouth / 44.0 / 20.0 / 5.0 / 6.0 / 8.0 / 1.0	Lists major and minor constituents of BR	No mention of potential exposure pathways	No mention of human and/or ecological toxicity	Table 3. Advantages and disadvantages of various method of disposal of BR (Jones and Haynes, 2011) Method / Advantages / Disadvantages Disposal of BR in lakes/sea / Investment cost on ponds is nil, reasonable investment in machinery for transportation. Less energy consumption. / Loss/recovery of caustic owing to no return of water. Dangerous to marine organisms in the long run. Dumped at a depth more than 25m and extensive pipeline requirements. Disposal of BR as dry mud / Easier reclamation process and rapid consolidation. Less space required and reduction in seepage. Reduction in the pumping of water (slurry). / High investment cost to concentrate the slurry and pumping. High evaporation climate required. High cost on earth moving equipment. High energy requires. BR drying in sun / Disposal area required is more than for dry disposal but less than for slurry. Reduce soluble soda losses. / Alternative required during rainy seasons. Disposal of BR as drained slurry / Less groundwater contamination. / High initial cost in sealing and draining of pond floor. Disposal of BR as conventional slurry / Caustic recovery is excellent. Transport cost is cheaper. Low cost investment on infrastructure. Natural surfaces can be used for providing banks. / Building ponds investment is higher. Requires enlargement of ponds/new ponds. More disposable area required. Time consuming, pollution hazard. Large pumping volume, slow rate of sedimentation, reclamation expensive.
Sheng-guo Xue	Industrial wastes applications for alkalinity regulation in bauxite residue A comprehensive review	2019	Bauxite residue is a highly alkaline material generated from the production of alumina in which bauxite is dissolved in caustic soda. Approximately 4-4 billion tons of bauxite residues are either stockpiled or landfilled, creating environmental risks either from the generation of dust or migration of filtrates. High alkalinity is the critical factor restricting complete utilization of bauxite residues, whilst the application of alkaline regulation agents is costly and difficult to apply widely. For now, current industrial wastes, such as waste acid, ammonia nitrogen wastewater, waste gypsum and biomass, have become major problems restricting the development of the social economy. Regulation of bauxite residues alkalinity by industrial waste was proposed to achieve 'waste control by waste with good economic and ecological benefits. This review will focus on the origin and transformation of alkalinity in bauxite residues using typical industrial waste; It will **propose key research directions with an emphasis on alkaline regulation by industrial waste,** whilst also providing a scientific reference point for their potential use as amendments to enhance soil formation and establish vegetation on bauxite residue disposal areas (BRDAs) following large-scale disposal.	At present, bauxite residue (BR) reuse is largely focused on valuable metal recycling, construction materials, and environmental restoration materials, production and manufacturing. Given the strong alkaline nature of BR which can cause production of alkali aggregates and corrosion of steel parts during the process of actual application, the utilization of BR is restricted. **The global re-use of BR is less than 10% due to its high pH (10-13)** and leachate production, making alkaline regulation the major hurdle affecting BR reuse. Industrial wastes such as acid, brine, waste water, and acid waste gas have been used to regulate BR alkalinity (i.e., dealkalization) which is also known as **'waste control by waste'.** The chemical composition of BR is mainly **Na2O, Al2O3, Fe2O3, SiO2, TiO2, and CaO.** **The production of alumina from bauxite generates alkaline substances which are divided into soluble and insoluble chemical alkali.** **Insoluble chemical alkali is mainly composed of sodium, cancrinite, calcite, hydrogarnet, diaspora, gibbsite and and tri-calcium aluminate.** Soluble alkali is generated from the reaction of caustic soda and bauxite which forms **sodium hydroxide, which is then converted into sodium aluminate and sodium silicate** and easily reacts with CO2 in the air and small amounts of SiO2 to generate **sodium bicarbonate and soluble sodium silicate.** There are two main methods of regulating alkalinity, one is to convert the insoluble alkali to soluble alkali, the other is to transform soluble alkali into a dissoluble substance by precipitation reaction, then subsequently suppress the dissolution of insoluble alkali. Given that management problems still exist for large quantities of industrial wastes as they are potentially hazardous materials, there is an opportunity to use these wastes as useful amendments to control and regulate BR alkalinity. Current methods of BR alkaline regulation using industrial waste include removal of alkali in BR using **waste acid neutralization via wastewater**; converting soluble alkali to soluble minerals via **brine neutralization**; using **CO2 and SO2** (from large-scale productions) to neutralize BR and; using **biomass** (biological and microbial activity!) to reduce BR alkalinity. With each of these methods carrying their own advantages, disadvantages, and limitations, it is recommended that moving forward, regulation of BR by industrial waste should be concerned with the technical and economic feasibility of the method, as well as the potential associated environmental impacts.	Lists major constituents of BR	No mention of potential exposure pathways	No mention of human and/or ecological toxicity	
Pei Lyu	Dealkalization processes of bauxite residue A comprehensive review	2021	Bauxite residue is a kind of strong alkaline waste produced in the production of alumina. Its long-term storage poses a potential threat to the environment. With the tightening of environment policies in various countries, the strong alkalinity of bauxite residue has become a bottleneck restricting the sustainable development of aluminum industry all over the world. **This review covers the composition characteristics of bauxite residue,** and describes the Bayer process in detail, where emphasis is put on the formation of alkaline substances in bauxite residue and its release process in long-term storage. This review focuses on several typical processes for the management of bauxite residue alkalinity in recent decades around the world. The phase transformation mechanisms, merits and limitations, as well as application status are discussed. The potential application values of these typical methods are evaluated based on process characteristics. The large amount and varied characteristics of bauxite residue determine that it is unrealistic to solve the dealkalization problem of all bauxite residue with one method. It is recommended that the appropriate dealkalization process of bauxite residue should be selected according to the characteristics of bauxite residue and regional resources, as well as the planning of subsequent application.	Given its high alkali and heavy metal content, long-term storage of bauxite residue (BR) not only occupies large plots of agricultural land, but also puts environments at risk. Leachates from BR landfills can **contaminate the surrounding soil and groundwater**, causing adverse environmental effects. Additionally, given that the particle size of BR is extremely fine, it **easily forms dust on the surface of the disposal area which can harm the surrounding communities and the downwind area**. In order to combat the increasingly serious environmental challenges, numerous innovative strategies have been proposed trying to re-utilize BR in effective and useful ways. The main remediation efforts for BR focus on recovery of value metals, production of construction materials, application as catalysts, etc. However, the strong alkalinity of BR limits the utilization of BR in these fields. Dealkalization of BR is necessary prior to following disposal or comprehensive utilization. In theory, the two main methods of dealkalization of BR is to convert the insoluble alkalis into soluble ones or convert soluble alkalis into insoluble ones by precipitation; however, in practice, both methods are combined. The most common dealkalization techniques include **acid neutralization (e.g., acid leaching and acid gas neutralization using CO2 and SO2); salt (ion) precipitation or displacement (e.g., seawater neutralization); gypsum remediation; pyrometallurgy; hydrometallurgy and; microbial-driven alkaline regulation**. Interestingly, the **University of Limerick and Rusal** have performed **successful rehabilitation with the addition of gypsum at the alumina refinery in Aughinish in Ireland**. The addition of gypsum to BR can not only reduce its alkalinity, but also alleviate the burden of soluble toxic elements on the aqueous environment, can increase the nutrients necessary for plant growth in the BR (such as Mg), and when coupled with organic amendments can improve the physical and chemical properties of BR leading to a more suitable substrate for plant growth. Each of the mentioned dealkalization methods have their own unique technical characteristics; however, these methods also have certain defects, which limits their large-scale commercial promotion. Selection of the appropriate dealkalization process for BR should consider BR characteristics, regional resource characteristics and subsequent application planning. It is recommended that continued scientific research focus on further understanding the dissolution behaviors of solid alkaline minerals in BR and the synergistic use of various wastes.	Lists major constituents of BR	Highlights the major exposure pathway of BR "given that the particle size of BR is extremely fine, it easily forms dust on the surface of the disposal area which can harm the surrounding communities and the downwind area".	No mention of human and/or ecological toxicity; however, although BR can leach into groundwater and cause adverse environmental effects, when dealkalinated and augmented with organics it can serve as a suitable substrate for plant growth	

LEAD AUTHOR	TITLE	DATE	ABSTRACT	SUMMARY OF PERTINENT POINTS	COPCs	EXCEPTIONS	EXPOSURE PATHWAYS	TOXICITY
REVIEWS ON HEALTH RISKS								
Daniel Evenski	Human Health Risk Assessment for Aluminium, Aluminium Oxide, and Aluminium Hydroxide	2007	Evaluates potential health effects from general exposures to aluminium in the environment. Concludes that health effects associated with oral exposure to aluminium in general, and the neurological (ALS) health endpoint in particular, deserve the greatest scrutiny.	Some studies have shown that lower aluminium exposures may contribute to Shaver's disease, a pulmonary fibrosis seen in workers in bauxite refining or exposed to finely divided aluminium powders [Kilduff, 1948, Arcida et al. 1989 and Lorrano et al. 1992]	- Reviews studies related to Al dust from bauxite refining	- Reviews studies related to occupational exposure	- Reviews studies related to inhalation exposure	- Exposure to Al dust may cause pulmonary fibrosis
A. Michael Donoghue	Health Risk Assessments for Alumina Refineries	2014	Objective: To describe contemporary air dispersion modeling and health risk assessment methodologies applied to alumina refineries and to summarize recent results. Methods: Air dispersion models using emission source and meteorological data have been used to assess ground-level concentrations ($\mu g/m^3$) of refinery emissions. Short-term (1-hour and 24-hour average) HCIs and annual average HCIs have been used to assess acute health, chronic health, and incremental carcinogenic risks. Results: The acute hazard index can exceed 1 close to refineries, but it is typically less than 1 at neighboring residential locations. The chronic hazard index is typically substantially less than 1. The incremental carcinogenic risk is typically less than 10^{-6}. Conclusions: The risks of acute health effects are adequately controlled, and the risks of chronic health effects and incremental carcinogenic risks are negligible around referenced alumina refineries.	Alumina refinery HRAs conducted to date have concentrated mainly on the air inhalation pathway, if a reasonable to confirm the HRA pathways to the inhalation route, is the knowledge that other pathways will not significantly affect the overall assessed risk level. - Alumina refinery sources may be divided into point and fugitive sources. Fugitive sources include: area sources, such as bauxite residue storage areas, cooling ponds, bauxite stockpiles, and loading and transfer areas, such as train- and ship-loading facilities. These types of sources also involve difficult measurement, estimation, and/or release intermittency challenges - Acute and chronic hazard indices (AHI and CHI) tend to be dominated by a few compounds or substances, with many other substances adding only very marginally to the cumulative hazard profile. For example, for criteria pollutants nitrogen dioxide, sulfur dioxide, and particulate matter (expressed as PM10) were found to comprise most of the AHI in each alumina refinery HRAs - In an assessment of the health risk from fugitive dust from bauxite residue storages (Nigeria refinery HRA, 2008), the contribution of PM10 was found to dominate the AHI. Constituent metals present in bauxite residue dust typically made up less than 2% of the AHI. The CHI and ICR results were small. These findings suggest that short-term PM10 exposures are the most relevant determinant of health risk in relation to bauxite residue storages, just as for many other sources of crustal dusts, such as unsealed roads, farming operations, or engineering construction activities. They also complement more recent findings from a study conducted after a bauxite residue impoundment failure in Hungary (Unknown et al, 2001) where red mud dust appears to be less hazardous to human health than urban particulate matter. - ICR estimates from cumulative lifetime exposures at neighboring residential properties, due to refinery and residue storage emissions, were found in the referenced studies to generally achieve the US EPA "de minimis" risk criterion of 1×10^{-6}, an indicator of negligible risk (nearly all receptors were well below this level, with a few cases just marginally above it). More than 95% of the ICR at the maximum receptor for the Nigeria refinery HRA was accounted for by formaldehyde, polycyclic aromatic hydrocarbons, chromium VI, acetaldehyde, and arsenic. - The results of HRAs at alumina refineries to date suggest that of the three types of health risks, acute, chronic and carcinogenic, only the risk of acute health effects is of any practical relevance. The ARI can exceed 1 close to refineries, but is typically less than 1 at neighboring residential locations. - Commonly concerns about air emissions from Wagerup refinery resulted in a comprehensive range of investigations, including intensive ambient air quality monitoring, air dispersion modeling, HRA, and complaints analyses. These investigations found that the risks of health effects were negligible.	- Nitrogen dioxide, sulfur dioxide, and particulate matter (expressed as PM10) comprise most of the acute hazard index (AHI) in alumina refinery HRAs - ARI for health risks from fugitive dust in bauxite residue storages mostly based on PM10 (metals less than 2%) - Short-term PM10 exposures drives health risk from bauxite residue storages	- Surrounding communities around Al refineries	- Inhalation of bauxite dust is considered to be the major exposure pathway considered for humans, where other pathways will not significantly affect overall risk level	- HRAs at alumina refineries suggest that of the three types of health risks, acute, chronic and carcinogenic, only the risk of acute health effects is relevant. The ARI can exceed 1 close to refineries, but is typically less than 1 at neighboring residential locations - Commonly concerns about air emissions from Wagerup refinery resulted in a comprehensive investigations: intensive ambient air quality monitoring, air dispersion modeling, HRA, and complaints analyses Found negligible risk to human health
W. M. Mayes	Advances in Understanding Environmental Risks of Red Mud After the Ajka Spill, Hungary	2016	In the 3 years since the 2010 Ajka red mud spill (Hungary), there have been 48 scientific studies assessing the key risks and impacts associated with the largest single release of bauxite-processing residue (red mud) to the environment. These studies have provided insight into the main environmental concerns, as well as the effectiveness of remedial efforts that can inform future management of red mud elsewhere. The key immediate risks after the spill were associated with the highly caustic nature of the red mud slurry and fine particle size, which once desiccated, could generate fugitive dust. Studies on affected populations showed no major hazards identified beyond caustic exposure, while red mud dust risks were considered equal to or lower than those provided by urban dusts of similar particle size distribution. The longer-term environmental risks were related to the saline nature of the spill material (salinization of inundated soils) and the release and the potential cycling of organism-forming metals and metalloids (e.g., Al, As, Cr, Mn, and V) in the soil–water environment. Of these, those that are soluble at high pH, inefficiently removed from solution during dilution and likely to be ecotoxicants at ambient pH are of chief concern (e.g., Mn and V). Various ecotoxicological studies have identified negative impacts of red mud–amended soils and sediments at high volumes (typically [5 %) on different test organisms, with some evidence of molecular level impacts at high dose (e.g., genotoxic effects on plants and mice). These data provide a valuable database to inform future toxicological studies for red mud. However, extensive management efforts in the aftermath of the spill greatly limited these exposure risks through bauxite neutralization and red mud recovery from the affected land. Monitoring of affected soils, stream sediments, waters and aquatic biota (fungi, invertebrates and fish) have all shown a very rapid recovery toward pre-spill conditions. The accident also prompted research that has also highlighted potential benefits of red mud use for utilitarian material recovery (e.g., Ga, Co, V, rare earths, inform), carbon sequestration, biofuel crop production, and use as a soil ameliorant.	**ENVIRONMENTAL PATHWAYS AFTER THE SPILL** - Physical characterization of the spill material showed a particle size distribution that fell predominantly within the PM10 class centered around 3–8 um. Only a small portion of the red mud was distributed within finer aerosol classes (PM2.5 and PM1 with diameters less than 2.5 and 1 um, respectively. This gave the spill material a similar distribution to urban dusts, with researchers concluding that no risks above that typically encountered with urban dusts would be anticipated (Unknown, 2011). - Continuous (15 min interval) monitoring of PM10 fraction aerosols at two locations within the spill zone for a year after the spill did not show any breaches in air quality limits other than those that could be ascribed to dusts from domestic biomass burning in winter months (Szalay, 2010). - Water. Red Mud Leachates. In the immediate aftermath of the spill, analysis of residual leachate release from the Ajka RMDA was characterized by extreme pH (13.1) and alkalinity (up to 6600 mg L-1 as $NaCO_3$), and enrichment of a range of potential elements of concern (Al, As, Cr, Mo and V that are soluble at high pH). Only for Mo, P, and V were significant proportions partitioned in truly dissolved phases and therefore were bioavailable. Speciation analyses of V in leachate showed it to be present in its most toxic, pentavalent form (as vanadate). - Soils and sediment. Soil/mud is retained in many potential contaminants (notably Al, As, Cr, Ni, and Cr). Found enhanced leaching of As, Cr, and Ni from red mud when in contact with organic-rich media because of DOC acting as a vector for trace elements. **HUMAN EXPOSURE PATHWAYS** - Except for the health hazard provided by the caustic nature of the spill material through dermal contact, no other major risks were identified (e.g., evidence of effects on immune systems, or toxicity). - Key short-term pathway after the spill for human exposure was via fugitive dusts. - Laboratory bioassays on rats exposed to short-term (24-day over 2 weeks) desiccated red mud dusts to assess each bacteria found mild respiratory symptoms developed , but these were deemed to pose no greater respiratory hazard than urban dust at comparable concentrations (Czuvek, 2012). - Direct monitoring of potentially exposed populations (i.e., clean-up workers) showed no short-term cytogenetic or genotoxic effects of exposure to the spill material. However, it is notable that exposure levels differed greatly in the exposed population group (50 to 800 h), and these authors emphasized the need for longer-term assessments should there be latency in response to those exposed to the red mud, which are currently ongoing (Szendy, 2010). - Potential contamination of groundwater supply wells: leachate from red mud-amended soil column in laboratory studies showed pore waters with concentrations of most contaminants below drinking water quality thresholds Table 2 Summary of key environmental risks identified after the Ajka red mud spill with an overview of estimated timescales of potential impact and current level of scientific understanding regarding Aspect of red mud creating potential risk | Key pathway(s) | Key receptor(s) | Timescale of potential impact: Days, Weeks, Months, Years | Level of understanding | Comment Fine particle size distribution (fugitive dusts) | Air | Humans | M | Short-term risks similar to urban dusts. Possible latency in response—long-term studies on exposed populations ongoing | very to	- Immediate risks after the spill were associated with the highly caustic nature of the red mud slurry and fine particle size, which could generate fugitive dust once dried.	- Surrounding communities following release of red mud	- Key short-term pathway after the spill for human exposure was via fugitive dusts - Potential contamination of groundwater supply wells: leachate from red mud-amended soil columns in laboratory studies showed pore waters with concentrations of most contaminants below drinking water-quality thresholds	- Studies on affected populations showed no major hazards beyond caustic exposure, while red mud dust risks were considered equal to or lower than those provided by urban dusts of similar particle size distribution.
Xue S Q, Li Y R, Guo Y	Environmental Impact of Bauxite Residue: A comprehensive review	2017	Bauxite residue is a solid waste in the industrial process of aluminium oxide, and it is characterized by high alkalinity and salinity and has so large volume of utilization. Presently, bauxite residue is still stored or dumped on land. The high rate of bauxite residue spill and pollution episode and the impact of bauxite residue seriously threaten sustainable development of alumina industry. On the basis of reviewing the literature in recent 30 years, this review summarizes the physical properties, chemical properties, and biological toxicity, focuses on the four dimensions of environmental impacts of bauxite residue, including the chronic and potential problems of disposal, utilization, and revegetation, and emphasizes the acute and sudden environmental risk to surrounding soil, water, and ecosystem with a typical bauxite residue repository failure case. Given the concerned problems of disposal and utilization of bauxite residue, future research directions are also discussed in this paper. This will provide a scientific reference for the large-scale disposal of bauxite residue and ecological rehabilitation and ensure the healthy development of alumina industry.	**CONSTITUENTS** $NaOH$, $AlO(OH)$, SiO_2, CaO, $NaSO_4$, TiO Heavy metals: As, Cr, Cd, Ig, Pb, V Radioactive elements: Th, Ra, Th, U and rare earth elements, alkaline minerals ([NMARSHCOH] [INaX or NaSi]), ([NMARSHCOH] [[CaCO3], CaMZ(SiO4)x(SE)12-6x, TCA:[CaMZ(SE)12], NaOH, NaCO3), NaAl(OH)4, EOH, ICEOS, Negative ions: SO_4^{2-}, $CO3^{2-}$,$HCO3^-$, Positive ions: Na^+, K^+, $Ca2+$, $Mg2+$ **SUMMARY OF PREVIOUS STUDIES:** (1) The inhalation of RSD did not alter the basal respiratory mechanism, whereas it led to greater Methacholine-induced responses in airway resistance, demonstrating the progression of mild hyper-responsiveness. Histopathological investigations revealed fine, granular particles in the alveolar macrophages, as evidence that RSD had reached the lower respiratory tract and induced mild inflammation around the alveoli and the pulmonary vasculature. The mild respiratory symptoms that developed following short-term exposure of healthy individuals to high concentrations of airborne RSD do not appear to pose a greater respiratory hazard than the inhalation of urban dust at a comparable concentration. (2) The mass size distribution of resuspended red mud dust is bimodal. Most of the mass is concentrated at or above the aerodynamically equivalent diameter (AED) of 10 μm, with a smaller secondary mode around 4 μm. The number size distribution is dominated by particles with diameters of about 2 μm. (3) A cross-sectional survey of 2804 employees in three alumina refineries was performed. Subjects exposed to alumina were marginally more likely to report work related wheeze and rhinitis (11.4%, 11.3%) compare to normal level (2.8%, 8.0%), but there were no associations seen between bauxite exposure and lung function. (4) If resources were taken, groundwater down 1 seem to be affected by red mud. This conclusion was based on a case study conducted in Ocska, the results showed that, in this case, it can be concluded that presence of red mud landfill Ocska in the near distance does not significantly affect the quality of water in Balaton lake.				

LEAD AUTHOR	TITLE	DATE	ABSTRACT	SUMMARY OF PERTINENT POINTS	COPCs	RECEPTORS	EXPOSURE PATHWAYS	TOXICITY
STUDIES ON RED MUD (INDUSTRIAL WASTE GENERATED DURING THE PROCESSING OF BAUXITE INTO ALUMINA)								
Czovek D,	Respiratory consequences of red sludge dust inhalation in rats	2011	The environmental disaster following flooding by red sludge in the Ajka region in Hungary poses a serious public health threat with particular concern regarding the potentially adverse respiratory effects of the inhalation of red sludge dust (RSD) The respiratory consequences of the inhalation of RSD obtained from field samples were investigated in rats Rats were either exposed to RSD at a high concentration (2 weeks, 8h/day), or kept in room air After the exposures, the airway resistance (R(aw)) and the respiratory tissues mechanics were measured under baseline condition, and following methacholine (MCh) challenges with the aim of establishing airway hyper-responsiveness (AH) Histopathology was performed to assess lung morphologic alterations The physical properties and the chemical composition of the RSD were also characterized The size distribution, chemical composition and topology of the RSD particles applied in our experiments were similar to those observed at the site of the disaster The inhalation of RSD did not alter the basal respiratory mechanics, whereas it led to greater MCh-induced responses in R(aw), demonstrating the progression of mild AH Histopathological investigations revealed fine, granular particles in the alveolar macrophages, as evidence that RSD had reached the lower respiratory tract and induced mild inflammation around the alveoli and the pulmonary vasculature The mild respiratory symptoms that developed following short-term exposure of healthy individuals to high concentrations of airborne RSD do not appear to pose a greater respiratory hazard than the inhalation of urban dust at a comparable concentration		- Study focuses on red sludge dust obtained from the field	- Study on rats	- Inhalation exposure to rats within chambers exposed to RSD at a high concentration (2 weeks, 8h/day), or kept in room air	- Inhalation of RSD did not alter the basal respiratory mechanics, whereas it led to greater MCh-induced responses in R(aw), demonstrating the progression of mild AH Histopathological investigations revealed fine, granular particles in the alveolar macrophages, as evidence that RSD had reached the lower respiratory tract and induced mild inflammation around the alveoli and the pulmonary vasculature The mild respiratory symptoms that developed following short-term exposure of healthy individuals to high concentrations of airborne RSD do not appear to pose a greater respiratory hazard than the inhalation of urban dust at a comparable concentration
Andras Gelencser	The Red Mud Accident in Ajka (Hungary): Characterization and Potential Health Effects of Fugitive Dust	2011	As a result of a tragic industrial accident, a highly alkaline red mud sludge inundated settlements and agricultural areas near Ajka, Hungary on October 4, 2010 One of the major concerns about the aftermaths of the accident is the potential health effects of vast amounts of fugitive dust from red mud sediment Thus, we studied the chemical and physical properties of particles of red mud and its respirable fugitive dust, and performed toxicity measurements Under unfavorable meteorological conditions dry red mud sediment could emit very high amounts of respirable alkaline particles into the air The number size distribution of fugitive dust peaks above 1 μm aerodynamic diameter; therefore, its inhalation is unlikely to affect the deep regions of the lungs No significant mineralogical or elemental fractionation was observed between the sediment and dust, with the major minerals being hematite, cancrinite, calcite, and hydrogarnet Although the high resuspension potential and alkalinity might pose some problems such as the irritation of the upper respiratory tract and eyes, based on its size distribution and composition red mud dust appears to be less hazardous to human health than urban particulate matter	**PURPOSE:** '- The objective of our study was to comprehensively characterize both the spilled red mud sediment and particulate matter (PM10) resuspended from it with special emphasis on the potential health hazard posed by inhalation of these particles '- An assessment of potential health effects of fugitive dust should consider a number of aspects that are related to the special properties of red mud, including its particle size distribution, highly alkaline character, and the potential toxicity of red mud itself and its constituents **RESUSPENSION POTENTIAL** '- The resuspended PM10 fraction of dried and pulverized red mud sediment was 0 99 m/m% (standard deviation 0 19) The concentration of PM(10-1) strongly depended on the amount of red mud that was available for resuspension '- The extremely high potential resuspension ratio (nearly 1 m/m%) is unprecedented among natural soils which usually have their value in the ppm range **ALKALINITY AND METALS** '- The specific alkalinity of the PM(10-1) fraction of resuspended dust was 3 7 μekv g-1 The concentrations of the measured metals (Cd, Co, Cu, Ni) were below the detection limit (10 ppb) '- The inhaled alkalinity from red dust is well below the recommended no-effect limit The alkalinity of the red mud dust is unlikely to cause severe acute or chronic symptoms in healthy adults **SIZE DISTRUBUTION** '- Most of the mass is concentrated at or above the aerodynamically equivalent diameter (AED) of 10 μm, with a smaller secondary mode around 4 μm The number size distribution is dominated by particles with diameters of about 2 μm The typical number size distribution of the red mud aerosol exhibits a pronounced peak in the range between optical diameters of 3 and 8 μm '- The typical mass size distribution of urban aerosol is bimodal, with one distinct peak in the 0 1-1 μm range (accumulation mode), and another in the 1-10 μm range (coarse mode) Particles in the coarse mode may originate from erosion, wind dispersion of road and soil dust and anthropogenic activities, for example the thermal- and motion-induced mobilization of road dust and vehicle emissions (from the abrasion of tires and brakes) '- The elements that presumably originate form the Earth's crust (Al, Si, Ca, Ti, and Fe) are typically associated with a single size mode with geometric mean aerodynamic diameters of 4-5 μm This mode almost perfectly matches the small secondary mode in the measured mass size distribution of red mud dust particles The maximum local deposition of inhaled particles in this mode occurs in the extrathoracic region of the respiratory tract with a mean depositional rate of about 70-80% Thus, most coarse particles in this size range are already trapped in nasal passages and do not enter the lungs Fortunately, the nucleation (ultrafine) mode (particles with AED <0 1 μm) of urban aerosol that is the most critical in terms of health effects is completely missing from the mass size distribution of fugitive dust of red mud If present, this fraction would get all the way through the alveoli and deposit with high efficiency there Particulate matter in the accumulation mode range, being absent from red mud dust but a major fraction of urban PM10, also has serious health implications in urban air in spite of the fact that its total depositional rate is rather low (<25%) in the entire respiratory system The severe health effects of particles of this size are due to their high mass concentrations in polluted urban air as well as a plethora of toxic, mutagenic, carcinogenic compounds that result from combustion or other anthropogenic activities, or form in photochemical processes The dominant size fraction in red mud dust that is typically much less significant in urban air except for special locations and/or circumstances, has only extrathoracic deposition It means that this fraction—no matter how large its concentration—can cause irritation of "only" the upper respiratory tract (and the eyes) '- Eye irritation was reported by residents of the affected area and workers involved in the cleanup in the weeks immediately following the spill **TOXICITY** '- No genotoxicity was observed using the SOS chromotest kit using PM10-1 resuspended dust '- The major minerals of the red mud are hematite, cancrinite, calcite, and hydrogarnet Calcite is a common mineral that is unlikely to cause any adverse health effects Although there is a large body of literature on the health effects of silicate minerals that occur in asbestiform varieties, we are not aware of any studies on the effects of cancrinite and hydrogarnet Both minerals occur in red mud as platy, lamellar crystals Thus, the fibrous habits that have been thought to be associated with the carcinogenic effects of some asbestiform silicates are absent '- The effects of inhaled hematite dust have been studied in the case of iron ore miners Among hematite miners in China a significant excess risk of non-malignant respiratory disease and of lung cancer was found However, a heavy exposure to radon, quartz dust, and diesel fumes in unventilated underground mines probably contributed to the high mortality of the miners, and the independent effects of exposure to hematite dust could not be evaluated Another study found no apparent health risks associated with hematite mining; in this study the miners were not exposed to significant radon concentrations, smoking was prohibited underground and diesel emissions were also absent Roentgenologic changes in the lung due to the deposition of inhaled iron-bearing particles is called siderosis and was observed in many occupational groups exposed to iron oxide fumes These changes of the lungs are generally regarded to be benign without having any influence on lung function or progressing to fibrosis '- EDS analysis of ~40 individual particles in the TEM suggest that transition metals other than Fe (such as Ti, Mn and Cr) are incorporated into the hematite structure '- Apart from the large resuspension potential and consequently large atmospheric concentrations under windy conditions, the fugitive dust from red mud does not appear to pose a serious health hazard for residents of the affected region	- Under unfavorable meteorological conditions dry red mud sediment could emit very high amounts of respirable alkaline particles into the air - No significant mineralogical or elemental fractionation was observed between the sediment and dust, with the major minerals being hematite, cancrinite, calcite, and hydrogarnet		- The number size distribution of fugitive dust peaks above 1 μm aerodynamic diameter; therefore, its inhalation is unlikely to affect the deep regions of the lungs - The dominant size fraction in red mud dust has only extrathoracic deposition It means that this fraction can cause irritation of "only" the upper respiratory tract (and the eyes)	- Although the high resuspension potential and alkalinity might pose some problems such as the irritation of the upper respiratory tract and eyes, based on its size distribution and composition red mud dust appears to be less hazardous to human health than urban particulate matter '- No genotoxicity was observed using the SOS chromotest kit using PM10-1 resuspended dust

LEAD AUTHOR	TITLE	DATE	ABSTRACT	SUMMARY OF PERTINENT POINTS	COPCs	RECEPTORS	EXPOSURE PATHWAYS	TOXICITY
Gundy	No short-term cytogenetic consequences of Hungarian red mud catastrophe	2013	Red mud is an industrial waste produced in the process of alumina extraction from bauxite with concentrated NaOH When the red mud-containing reservoir collapsed in Ajka Alumina Plant Hungary in October 2010, the most serious immediate effects were caused by the high alkalinity (pH ≥ 13) of the flood Many persons suffered burn-like damage to tissues and contact with caustic desiccated ultra-fine dust with traces of toxic metals also caused irritation of upper respiratory tract and eyes This catastrophe was unique from the point of view of genotoxic effects as well Therefore cytogenetic examinations were carried out on inhabitants, either with burns (17 persons) or on those inhaling desiccated caustic dust (42 persons) Chromosomal aberration (CA) analysis and bleomycin (BLM)-sensitivity assays, as possible markers of effects, were studied in peripheral blood lymphocytes of persons within 4-6 weeks following the catastrophe Controls were matched for age, sex and smoking habits, and also places of residence with different constituents of air pollution either from rural (59 persons), or from urban environments (59 persons) Neither spontaneous rate of CAs (1 47% vs 1 69%) nor BLM-induced in vitro chromosomal breakage (0 79 vs 0 83 break/cell) showed elevated rates when cytogenetic biomarkers of genotoxicity were compared between controls and exposed persons Time spent in cleaning did not affect cytogenetic changes either (R(2) = 0 04) BLM-induced mutagen sensitivity was similar in exposed and control persons (27 1% vs 30 5%) It seems that the red mud exposure does not appear to pose an immediate genotoxic hazard on residents when measured with cytogenetic methods We recommend, however, that those involved in clean-up activities should be followed closely not only for overall health, but also for further genotoxic risk assessment, because the long-term hazards of ultra-fine fugitive dust particles with alkalinity of residual NaOH in red mud are still unknown		- Red mud dust following spill from Al refinery	- Residents in the surrounding communities	- Inhalation exposure	- Serious immediate effects were caused by the high alkalinity (pH ≥ 13) of the flood Many persons suffered burn-like damage to tissues and contact with caustic desiccated ultra-fine dust with traces of toxic metals also caused irritation of upper respiratory tract and eyes - The red mud exposure does not appear to pose an immediate genotoxic hazard on residents based on cytogenetic studies in peripheral blood lymphocytes undertaken on 59 civil residents, 4–6 weeks after the exposure to the red mud
Banu Ozden	Investigation of bauxite residue (red mud) in terms of its environmental risk	2019	This research describes the method of neutron activation analysis (NAA) and Compton suppression for determination of some toxic elements in red mud (collected from Eti Seydisehir Aluminium Plant in Turkey) Furthermore, short-term leaching tests of elements were undertaken on red mud to evaluate in terms of the environmental impact Morphological characterizations and qualitative element composition of red mud were also performed by SEM–EDX analysis Fe, Al, Na, Ti and Ca contents in red mud were found significantly high It can be concluded that some toxic elements may not easily mobile under the environmental conditions	**BACKGROUND** - Red mud which is an insoluble fine grained waste material produced by digestion of bauxite ore during the production of alumina contains toxic heavy metals Red mud mainly consists of silicon, aluminum, iron and titanium oxide phases and some metals such as vanadium, scandium, gallium and calcium in different proportions dependent on the country of origin of the bauxite ore The distribution of trace elements in bauxite depends on a number of factors, such as the bauxite age, iron contents and mineralogy The accumulation and reduction/elimination of waste material is one of the main essential issues for the aluminum industry due to its large amounts of red mud production The aluminum industry may be one of the main sources of increased natural radioactivity and toxic elements in the environment by the reason of the large areal requirements for red mud disposal ponds Due to the high alkalinity, red mud is extremely corrosive and is damaging to the environment [7, 8] Therefore, red mud should be considered a hazardous waste material in terms of its environmental impact - The amount of toxic elements discharged to the environment from red mud depends on a number of factors, such as the origin of the bauxite ore, the amount of red mud left over from the industry, concentrations in the residue and metal leaching features of this material under environmental conditions This study provides new data on some toxic elements in red mud and leachate samples in order to find out the enrichment of these elements and leaching characteristics **ENVIRONMENTAL CONCENTRATIONS IN RED MUD AND LEACHATE SAMPLES** - The major elements in red mud samples (from an Al plant in Turkey) are Fe and Al, followed by Na, Ti and Ca Other elements such as , Ce, Cr, La, Mn, Ni, Nd, Sc, Th, U, V and Zr has smaller concentrations - Bauxite deposits are classified related to their formation in three main categories: (1) lateritic bauxite deposits, (2) karst bauxite deposits and (3) Tikhvin-type deposits The collected red mud sample represents karst bauxite type which contains relatively high amounts of rare earths elements - Except for arsenic and uranium, the other elements were not detected in both of the leachate scenarios, where leachate tests were based on pH of natural rainwater (5 5) and ASTM water (2 9) Arsenic concentrations from rainwater leaching found to be higher than WHO drinking water limits - The immobility of both toxic elements may be due to pH and the fact that red mud contains a large amount of Fe and Al oxides and hydroxides that have large surface area and high affinity in order to adsorb metals - Work conducted on the characterization of red mud has shown that pH value of red mud decreased with duration of storage time A similar study on the mobility of metals in red mud has concluded that the potential release of metals from red mud could be higher than previously thought if it is stored for long periods	- The major elements in red mud samples (from an Al plant in Turkey) are Fe and Al, followed by Na, Ti and Ca Other elements such as , Ce, Cr, La, Mn, Ni, Nd, Sc, Th, U, V and Zr has smaller concentrations		- - Except for arsenic and uranium, the other elements were not detected in both of the leachate scenarios, where leachate tests were based on pH of natural rainwater (5 5) and ASTM water (2 9) Arsenic concentrations from rainwater leaching found to be higher than WHO drinking water limits -The immobility of both toxic elements may be due to pH and the fact that red mud contains a large amount of Fe and Al oxides and hydroxides that have large surface area and high affinity in order to adsorb metals	

APPENDIX

B NON-HAZARDOUS CLASSIFICATION OF BAUXITE RESIDUE WASTES

RUSAL
AUGHINISH

Classification of Farmed Bauxite Residue (01 03 09) as Non Hazardous at Rusal Aughinish Alumina Limited

Date: **September 2015**
Updated: **February 2020**

RUSAL
AUGHINISH

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Glossary

Abbreviations/Symbols	
RAAL	Rusal Aughinish Alumina Ltd.
BRDA	Bauxite residue disposal area
ECHA	European Chemicals Agency
EU	European Union
ha	Hectare
Mt/yr	Million tonnes per year
IEL	Industrial Emissions License
HP	Hazardous Property
EWC	European Waste Catalogue
EPA	Environmental Protection Agency
CLP	Chemicals, Labelling and Packaging

1. Executive Summary

Rusal Aughinish Alumina Limited (RAAL) is the largest Alumina refinery in Europe with an annual production capacity of 1.95mt/yr of alumina *via* the Bayer process. The major waste stream of the Bayer process is bauxite residue. Bauxite residue undergoes numerous stages of washing and filtration prior to discharge to the Bauxite Residue Disposal Area (BRDA). At RAAL a process of enhanced atmospheric carbonation termed "bauxite residue farming" has been developed to minimise the pH of deposited bauxite residue to the BRDA. Bauxite Residue farming reduces the residue pH below 11.5.

Farmed bauxite residue is the terminology applied by RAAL to describe bauxite residue which has undergone a process of partial neutralisation. Within the Alumina Industry bauxite residue may also be termed red mud.

This report summarises an assessment of RAAL farmed bauxite residue based on the following legislation;

1. EU Waste Framework Directive (2008/98/EC),
2. Commission Decision of 18 December 2014, amending Decision 2000/532/EC on the list of waste pursuant to Directive 2008/98/EC of the European parliament and of the Council (2014/955/EEC)
3. Commission Regulation (EU) No 1357/2014 of 18 December 2014, replacing Annex III to Directive 2008/98/EC of the European Parliament and of the Council on waste and repealing certain Directives.
4. Council Regulation (EU) 2017/997 of 8 June 2017 amending Annex 111 to Directive 2008/98//EC of the European parliament and of the Council as regards the hazardous property HP 14 'Ecotoxic'.
5. Extractive Waste Directive (2006/21/EC).

Summation of the Hazard statement codes for each compound present in farmed bauxite residue shows no threshold is exceeded for any of the hazard properties (HP). **Therefore, farmed bauxite residue is non-hazardous.**

The non-hazardous waste code '01 03 09 red mud from alumina production other than the wastes mentioned in 01 03 10', is assigned to RAAL farmed bauxite residue under 2014/955/EU Updated List of wastes.

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2. Site Description

The RAAL refinery is located on Aughinish Island, on the southern shore of the Shannon Estuary 33 kilometres west of Limerick city between the towns of Askeaton and Foynes. The plant commenced operation in 1983 and today has a production capability of 1.95mt/yr alumina. It sources bauxite from Guinea, Brazil and Guyana.

3. Storage Area Design

The bauxite residue is deposited in an engineered facility called the Bauxite Residue Disposal Area that has been designed to ensure the long-term stability of the residue. The BRDA is formed by construction of perimeter embankments: an inner and outer embankment with a perimeter intercept channel in between. The bauxite residue is retained by a perimeter stack wall constructed of rockfill, which is raised consecutively in 2 metre vertical stages (upstream embankment raising). There is also a flood tidal defence berm between the BRDA and the Shannon Estuary foreshore that protects the BRDA from wave and tidal erosion.

The bedrock of the island area is Carboniferous Limestone. There are outcrops of this limestone on the northern and eastern area of the Aughinish Island. A discontinuous layer of glacial till is also present. The estuarine sediments are on average 8 metres thick particularly adjacent to the estuary where the BRDA is located.

The BRDA is constructed with engineered composite liners on the underlying strata. All perimeter intercept channels are also lined with this engineered composite liner.

The BRDA has been designed and is operated to ensure that all water run-off from the facility is collected and treated before discharge, and that any subsurface seepage from beneath the facility is prevented. The water management system provides for collection and treatment of surface water runoff and leachate from the BRDA.

4. Bauxite Residue Disposal Area Operation

The deposition method employed at RAAL is dry stacking of washed, filtered residue which is pumped by positive displacement pumps to the BRDA at 58% solids, where the bauxite residue is layered at a slope of approximately 2.5%, then subsequently farmed to increase the percent solids to 74%. The combined BRDA area is effectively a large mono-cell and is divided into 46 operational areas or cells to facilitate short deposition times and thin layer deposition.

Partial neutralisation of the bauxite residue by atmospheric carbonation through farming produces a residue with pH below 11.5 which is suitable for remediation and revegetation [1]. This post deposition atmospheric carbonation *via* farming process is outlined below.

4.1 Amphirolling

Bauxite residue at RAAL undergoes 3 stages of counter current washing in large settling vessels. The residue is then filtered on 8 large drum filters where it undergoes a final stage of washing with hot clean condensate. After vacuum filtration the residue is diluted with water, sheared and thinned in an agitated tank and then pumped as a 58% solids paste to the BRDA. In this state the deposited bauxite residue cannot yet be traversed by conventional machinery and first must be dewatered and compacted. An amphibious vehicle called an amphirol is employed to carry out this de-watering and compaction.

The amphirol travels using scrolls which act as semi-flotation devices to allow the vehicle to move through the residue. As the amphirol travels it compresses the residue and creates tracks or furrows. These furrows allow the water which has been “squeezed” from the residue to drain along the sloping stack towards the perimeter wall of the cell and into the perimeter channel. Amphirolling for compaction can require up to 20 travel times.



Figure 1: Bauxite residue farming and atmospheric carbonation process at RAAL

4.2 Grading

Once the residue has compacted to >70% solids by multiple passes of the amphirol, the residue surface is then graded by a bulldozer to level the surface and generate a constant gradient from the discharge (high point) to the perimeter wall (low point). This makes the residue suitable for conventional agricultural machinery to travel and operate on its surface. In this condition the dewatered residue is also capable of being broken into small lumps to allow for exposure to CO_2 in the air. The grading also establishes the base for the subsequent residue layer to be deposited.

4.3 Ripping

Once the residue surface has been re-graded the compacted residue layer must be "ripped" to open the 'compacted residue' and allow it to be easily worked by the other machinery used in the carbonation process. A tractor subsoiler attachment is used to rip and break the compacted residue layer into large lumps. The subsoiler has a working depth of 40-45cm.

4.4 Ploughing and Harrowing

The 'ripped' residue lumps must then be broken into smaller lumps and aerated a number of times to carbonate and neutralise any residual caustic. This is achieved by an efficient harrowing unit called a 'spader'. Once the subsoiler has loosened the bauxite residue layer, a tractor-driven 'spader' digs into and harrows the broken up residue lumps. Approximately 10-16 passes of the spader at up to 2 passes per day bring about sufficient exposure and carbonation to reduce bauxite residue pH below 11.5. The harrowing process using a spader can normally be conducted in a period of 1-2 weeks.

4.5 Final Compaction

While a bauxite residue layer is being harrowed a lot of voidage is created within the active layer. This is the mechanism by which the residue is exposed to atmospheric CO_2.

Once carbonation is completed as evidenced by pH measurements of samples from the cell, the area is then re-graded using a bulldozer to remove any depressions. Finally the cell is re-compacted using a vibrating plate compactor or a vibratory roller to maximise in-situ compaction and prepare the cell for the subsequent layer of residue. Through amphirolling, harrowing and final re-compaction the initial 40 cm deep layer of residue is compacted into a 30 cm deep well-compacted and partially neutralised bauxite residue layer. The cell is then ready for the subsequent layer of residue.

5. EU Extractive Waste Classification Legislation

There is a legislative framework within the European Union (EU) that specifies precise criteria for classification of waste as hazardous or non-hazardous. Bauxite residue disposal and its classification are directly subject to the following legislation;

- EU Waste Framework Directive (2008/98/EC),
- Commission Decision of 18 December 2014, amending Decision 2000/532/EC on the list of waste pursuant to Directive 2008/98/EC of the European parliament and of the Council (2014/955/EEC)
- Commission Regulation (EU) No 1357/2014 of 18 December 2014, replacing Annex III to Directive 2008/98/EC of the European Parliament and of the Council on waste and repealing certain Directives.
- Council Regulation (EU) 2017/997 of 8 June 2017 amending Annex 111 to Directive 2008/98//EC of the European parliament and of the Council as regards the hazardous property HP 14 'Ecotoxic'.
- Extractive Waste Directive (2006/21/EC).

Design, operation and the ultimate closure of the RAAL BRDA for farmed bauxite residue storage is licensed under the Extractive Waste Directive 2006/21/EC. The BRDA is classified as a Category A facility under the Extractive Waste Directive due to its scale and location adjacent to a Special Area of Conservation. This classification ensures that the design and operation provides the highest level of environmental protection possible. RAAL is required by its Industrial Emissions License (IEL P0035-06) to minimise the pH of deposited residue. To achieve this, a process of enhanced atmospheric carbonation termed 'Bauxite Residue Farming' has been developed.

In terms of waste classification the Extractive Waste Directive refers to the Hazardous Waste classification methodology and thus farmed bauxite residue hazard classification is addressed by Hazardous Waste legislation. Annex II of this Extractive Waste Directive states that…"*classification of the waste shall be according to the relevant entry in Directive 2000/532/EC with particular regard to its hazardous characteristics"*.

Although the Chemicals, Labelling and Packaging (CLP) legislation is not directly applicable to waste (*ECHA Guidance on the Application of the CLP Criteria, 2015*) [2] there are moves to harmonise the Waste and CLP legislation. The CLP legislation also details the specific concentration limits for hazardous compounds and describes the tests required for direct Hazardous Property (HP) testing of the waste to directly determine if a waste exhibits a particular HP.

The methodology to classify a waste is as follows.

- Is the waste a 'Special Waste' subject to its own specific legislative provisions and therefore excluded from the scope of general Hazardous Waste legislation e.g. radioactive waste or decommissioned explosives.
  Note: While bauxite residue disposal is primarily legislated via the Extractive Waste Directive 2006/21/EC, its waste classification follows the Hazardous Waste legislation.

- Is the Waste already coded/classified in the EU 'List of Wastes'?
  Note: Regarding bauxite residue there are two possible codes, one being hazardous and the other being non-hazardous. Thus an assessment of each bauxite residue type from each Alumina Refinery BRDA is required to determine which code on the official EU 'List of Wastes' should be applied to the bauxite residue in question.
- Determine the detailed composition of the waste mixture down to 0.1% concentration.
  Note: It is necessary to identify the specific compounds present in the waste rather than employ elemental analysis.

- Determine the contribution to Hazardous Property of each compound present in the waste

- For each compound present in the waste identify if it is classified as dangerous i.e. is there an associated Risk phrase and Hazardous Property (HP) associated with that compound.

- For each HP (there are 15 potential HPs in total) sum all of the % compositions of compounds that contribute to the HP in question.

- Determine if the summation of the % compositions contributing to any specific HP causes the waste to exceed the thresh-hold for that HP. If so the bauxite residue would then be classified as having that HP and must be classified as hazardous due to the HP in question unless direct HP testing confirms that the waste is not hazardous.

6. Farmed Bauxite Residue Classification

6.1 Farmed Bauxite Residue Analysis

Full compositional analysis is carried out quarterly on farmed bauxite residue at RAAL employing such techniques as X-Ray Fluorescence, Thermo Gravimetric Analysis, Differential Scanning Calorimetry, Ion Chromatography, Atomic Absorption Spectroscopy and Inductively Coupled Plasma.

The principal sources of information for Hazard statement codes were:

- Safety Data Sheets from Sigma Aldrich
- Safety Data sheets from other large companies in the absence of a Sigma Aldrich SDS.
- Review of ECHA

Full Chemical Analysis				
Compound	**Formula**	**w/w%**	**Hazard Statement Code**	**CAS No.**
Moisture	Free H2O	21.9	*	
Aluminum Goethite	(Fe,Al)2O3.H2O	20.9	*	1310-14-1
Hematite	Fe2O3	18.75	*	1317-60-8
Calcium Cancrinite	3(Na2O.Al2O3.2SiO2)2CaCO3	12.15	*	12172-98-4
Bayer Sodalite	3(Na2O.Al2O3.2SiO2.2H2O)0.8Na2CO3 .0.2Na2SO4	5.35	*	1344-00-9
Gibbsite	Al2O3.3H2O	4.85	H319	21645-51-2
Perovskite	CaTiO3	4.1	*	12049-50-2
Anatase and Rutile	TiO2	4.1	H332, H319, H335, H315	1317-70-0/ 13463-67-7
Hydrogarnet	3CaO.Al2O3.SiO2.4H2O	2.95	*	68131-78-8
Boehmite	Al2O3.H2O	2.15	*	1318-23-6
Quartz	SiO2	0.7	H372, H373	14808-60-7
Sodium Carbonate	Na2CO3	0.31	H319	497-19-8
Zircon	ZrSiO4	0.3	H332, H319, H335, H315	10101-52-7
Carbonate Apatite	5.2CaO.0.8Na2O.2.5CO2.P2O5	0.2	H319	471-34-1
Gypsum	CaSO4.2H2O	0.15	*	10101-41-4
Sodium Sulphate	Na2SO4	0.075	*	7757-82-6
Sodium BiCarbonate	NaHCO3	0.045	H315, H319	144-55-8
Sodium Fluoride	NaF	0.02	H300 (cat 2), H315, H319	7681-49-4
Sodium Aluminate	NaAl(OH)4	0.005	H290, H314	11138-49-1
Sodium Hydroxide	NaOH	0	H314	1310-73-2
Trace Metals - Semi Quantitative XRF				
Chromium Trioxide	Cr2O3	0.2	*	1308-38-9
Vanadium Pentoxide	V2O5	0.2	H302, H332,H318, H341, H361, H335, H372, H411	1314-62-1
Magnesium Oxide	MgO	0.12	*	1309-48-4
Cerium Oxide	CeO	0.02	*	1306-38-3
Potassium Carbonate	K2CO3	0.03	H302, H335, H315, H319	584-08-7
Manganese Oxide	MnO	0.035	*	1344-43-0
Gallium Trioxide	Ga2O3	0.0085	*	12024-21-4
Arsenic Trioxide	As2O3	0.01	H300, H314, H350, H400, H410	1327-53-3
Niobium Pentoxide	Nb2O5	0.014	H315, H319, H335	1313-96-8
Zinc Oxide	ZnO	0.005	H410	1314-13-2
Lead oxide	PbO	0.007	H302, H332, H360Df, H373, H410	1317-36-8
Yttrium Trioxide	Y2O3	0.0095	H315, H335	1314-36-9
Strontium Oxide	SrO	0.0095	H314	1314-11-0
Copper Oxide	CuO	0.004	H400, H412	1317-38-0
Thorium Oxide	ThO	0.01	H301, H311, H331, H350, H373	1314-20-1

Table 1: Full Chemical Analysis

*No hazard statement code classified

6.2 Waste Classification

In the case of farmed bauxite residue there are two possible waste codes which can be assigned under 2014/955/EU Updated List of wastes amending (2000/532/EC).

- 01 03 10* red mud from alumina production containing hazardous substances other than the wastes mentioned in 01 03 07 and
- 01 03 09 red mud from alumina production other than the wastes mentioned in 01 03 10

Where * denotes hazardous waste.

The classification of the waste is based on the application of the updated Annex to Waste Framework Directive (1357/2014) to the compositional analysis of the farmed bauxite residue under hazardous properties HP1-15. A waste classification tool has been developed and released by environmental protection Agency (EPA) Ireland based on the legislation and is the basis for classification of farmed bauxite residue [6]. The commission regulation 1357/2014 states that the "*attribution of the hazardous property HP 14 is made on the basis of the criteria laid down in Annex VI to Council Directive 67/548/EEC*." As such, the hazard property HP14 is assessed based on this criterion according to the waste classification tool released by EPA, Ireland.

Table 2 summarises the hazard statement codes in each of the hazard property category compared to the threshold for each category based on the typical farmed bauxite residue composition in Table 1 above. The Analysis of the compositional data shows that RAAL farmed bauxite residue does not exceed the concentration limits of any of the hazardous properties and is classified as non-hazardous.

Hazard Property	Hazard Class	Hazard Code	Threshold	Sample	Hazardous
HP1	Explosive	H200	Y/N	N	N
		H201	Y/N	N	N
		H202	Y/N	N	N
		H203	Y/N	N	N
		H204	Y/N	N	N
		H240	Y/N	N	N
		H241	Y/N	N	N
HP2	Oxidising	H270	Y/N	N	N
		H271	Y/N	N	N
		H272	Y/N	N	N
HP3	Flammable	H220	Y/N	N	N
		H221	Y/N	N	N
		H222	Y/N	N	N
		H223	Y/N	N	N
		H224	Y/N	N	N
		H225	Y/N	N	N
		H226	Y/N	N	N
		H228	Y/N	N	N
		H242	Y/N	N	N
		H250	Y/N	N	N
		H251	Y/N	N	N
		H252	Y/N	N	N
		H260	Y/N	N	N
		H261	Y/N	N	N
HP4	Irritant	H314	1	0	N
		H318	10	0	N
		H315 +H319	20	8.95	N
HP5	Specific target Organ Toxicity	H370	1	0	N
		H371	10	0	N
		H335	20	4.1	N
		H372	1	0.7	N
		H373	10	0.7	N
		H304	10	0	N
HP6	Acute Toxicity	H300 (cat 1)	0.1	0	N
		H300 (cat 2)	0.25	0	N
		H301	5	0	N
		H302	25	0	N
		H310	0.25	0	N
		H310	2.5	0	N
		H311	15	0	N
		H312	55	0	N

Hazard Property	Hazard Class	Hazard Code	Threshold	Sample	Hazardous
		H330	0.1	0	N
		H330	0.5	0	N
		H331	3.5	0	N
		H332	22.5	4.4	N
HP7	Carcinogenic	H350	0.1	0.02	N
		H351	1	0	N
HP8	Corrosive	H314	5	0	N
HP9	Infectious	**	Y/N	N	N
HP10	Toxic for Reproduction	H360	0.3	0.007	N
		H361	3	0.2	N
HP11	Mutagenic	H340	0.1	0	N
		H341	1	0.2	N
HP12	Release of Acute Toxic gas	UEH029	Y/N	N	N
		UEH031	Y/N	N	N
		UEH032	Y/N	N	N
HP13	Sensitising	H317	10	0	N
		H334	10	0	N
HP14	Ecotoxic	R50 and R51	1	0.08	N
		R50 and R53	25	0	N
		R52	25	0	N
		R53	25	0.2	N
HP15	Waste capable of exhibiting a hazardous property listed above not directly displayed by the original waste	H205	Y/N	N	N
		EUH001	Y/N	N	N
		EUH019	Y/N	N	N
		EUH044	Y/N	N	N

List of Wastes Entry	Hazardous Y/N	Description
01 03 09	N	Red mud from alumina production other than the wastes mentioned in 01 03 10 01

Table 2: Classification of RAAL Farmed bauxite residue

7. Conclusion

At RAAL bauxite residue is thoroughly washed and significantly dewatered prior to disposal in the licenced 'state of the art' BRDA. A process of enhanced atmospheric carbonation termed "bauxite residue farming" has been developed at RAAL to carbonate any residual caustic and minimise the pH of the deposited bauxite residue. This bauxite residue farming reduces the pH of farmed bauxite residue below 11.5. Bauxite residue farming also improves the compaction and dry density of the residue increasing storage efficiency.

This assessment of RAAL farmed bauxite residue applies the current EU legislation as specified by the EU Waste Framework Directive (2008/98/EC), the Hazardous Waste Directive (2000/532/EC) and the Extractive Waste Directive (2006/21/EC). Summation of the Hazard statement codes for each compounds present in farmed bauxite residue shows no threshold is exceeded for any of the hazard properties (HP) and that farmed bauxite residue is non-hazardous.

8. References

1. Kirwan, L.J., Hartshorn, A., McMonagle, J.B, Fleming, L, and Funnell, D. *Chemistry of bauxite residue neutralisation and aspects to implementation*, International Journal of Mineral Processing, 119, 40-50 (2013).
2. European Chemicals Agency. *Guidance on the Application of the CLP Criteria*, Version 4.1, June 2015. http://echa.europa.eu/documents/10162/13562/clp_en.pdf
3. Environmental Protection Agency, Ireland. *Waste Classification, List of Waste & Determining if Waste is Hazardous or Non-hazardous*, 2019. http://www.epa.ie/pubs/reports/waste/stats/wasteclassification/
4. 2018/C 124/01 Commission notice on technical guidance on the classification of waste. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2018:124:FULL&from=EN

29.9.2014

NOTICE TO MEMBERS

Subject: Petition 0010/2006 by Patrick Culhane (presumably Irish), on behalf of Cappagh Farmers Support Group, on Aughinish Alumina Plant in Ireland

1. Summary of petition

The petitioner is concerned with the pollution from the Aughinish Alumina Plant at Askeaton in Co. Limerick Ireland and with the actions of the relevant authorities, especially the Environmental Protection Agency (EPA) in allowing and facilitating the company's continued breaches of environmental law. The petitioner expressed concern about the results of an environmental audit in 2003 where EPA has found that Aughinish Plant produced emissions which were seven times higher than the permitted level and was unable to account for 7,000 tonnes of toxic caustic solution. The petitioner argues that EPA hadn't taken appropriate actions in protecting the local population and environment.

2. Admissibility

Declared admissible on 4 April 2006. Information requested from the Commission under Rule 192(4).

3. Commission interim reply, received on 30 August 2006.

The petitioner raises concerns about the actions taken by the Irish Environmental Protection Agency (EPA) following the licence audit report carried out in August 2003 by the EPA on the site of the Aughinish Aluminia Plant which produces alumina from bauxite.

The 2003 audit on the compliance with the permit issued by the competent authorities in May 1998 highlighted a number of non-compliances as well as some issues where further actions were required. This relates in particular to the emission of particulate matters and sulphur

dioxids, the management of waste, the losses of caustic solution and the soil contamination. The petitioner considers that the EPA has not taken the appropriate enforcement actions to protect local population and the environment.

This installation is subject to Directive 96/61/EC concerning integrated pollution prevention and control[1]. According to this Directive, competent authorities are required to determine, for each installation, an integrated permit based on best available techniques to ensure a high level of protection of the environment taken as a whole. Competent authorities are also required to ensure that the conditions of the permit are complied with by the operator when operating the installation.

The specific installation addressed by the petitioners was in operation before October 1999 and is therefore considered as "existing" in the term of the Directive. Member States have a transition period until 30 October 2007 to ensure that existing installations are brought into full compliance with the Directive. The Commission understands from the information available that the current permit of the installation concerned issued under Irish legislation is currently subject to a review to bring this installation into compliance with Directive 96/61/EC.

The Commission will further investigate this issue with the Irish authorities. The Commission will also seek information from the Irish authorities on the implementation of other Community legislation which may be already applicable to this specific installation. This relates in particular to waste, air quality and groundwater legislation.

4. Further Commission reply, received on 25 January 2007.

Following the request of the Commission, the Irish authorities have provided the following information on the operation and control of the Aughinish Aluminia installation.

The Irish authorities have confirmed that the installation is subject to Directive 96/61/EC concerning integrated pollution prevention and control[2] (IPPC). This installation is considered as an existing installation under the terms of the IPPC Directive. The competent authorities have therefore a transition period until 30 October 2007 to ensure that this installation is brought into full compliance with the Directive. According to the Irish authorities, the current permit of the installation is being reviewed and will be amended, if deemed necessary, in order to ensure full compliance by the deadline of 30 October 2007.

As regards the implementation of other Community legislation already applicable to this specific installation, the Irish authorities provided information on the application of the waste, air quality and groundwater legislation.

The Irish authorities also informed the Commission about the enforcement actions taken and the improvement made to the installation following the non-compliance issues highlighted in the audit carried out in 2003 by the Irish Environmental Protection Agency (EPA). This related in particular to the emission of particulate matters and sulphur dioxides, the

[1] OJ L 257, 10.10.1996, p. 26.
[2] OJ L 257, 10.10.1996, p. 26.

management of waste, the losses of caustic solution as well as the soil and groundwater contamination.

As a conclusion and on the basis of the information submitted by the petitioner and the Irish authorities, the Commission has not identified a breach of Community legislation regarding the operation of the installation concerned. Should the petitioner provide detailed information enabling the Commission to assess these issues in relation to the above-mentioned legislation, the Commission will then be able to investigate this matter further.

5. Further Commission reply (REV. II), received on 18 July 2011.

At the time of the previous communication, the Commission had not identified any problem of compliance from the information submitted. However, since then, it has received additional information from the petitioner, including information drawing attention to the fact that, like the Hungarian aluminium smelter involved in the red mud disaster, the Aughinish facility includes an extensive red mud storage area.

In light of the above, the Commission has submitted a further request for information to the Irish authorities. The Commission has requested information from the Irish authorities to assess the operating conditions, the management of the waste, the losses of caustic solution as well as the soil and groundwater contamination at the installation, as well as possible enforcement actions taken.

6. Commission reply (REV. III), received on 17 February 2012

At the time of the last communication, the Commission reported that it had requested information from the Irish authorities to assess the operating conditions, the management of the waste, the losses of caustic solution, as well as the soil and groundwater contamination at the Aughinish facility, together with the possible enforcement actions taken.

The Commission received a reply from the Irish authorities on 13 July 2011. The Commission's analysis of the Irish response can be summarised as follows:

- Ireland considers that the installation falls under the scope of Directive 2006/21/EC on Management of Waste from Extractive Industries. This directive provides for a transitional period until 1 May 2012, to bring all permit conditions in compliance with the Directive's provisions. After the expiry of this period, the Commission will contact the Irish authorities again to check what adaptations have been achieved and how some of the key requirements have been met;

- Ireland confirms that the installation uses the dry storage method for the disposal of red mud (which is also now the one being used by MAL Zrt. in Hungary following the red mud accident on 4 October 2010). The operator is also required to implement a dust control regime, as well as dust and ambient air monitoring;

- Between 1 January 2006 and 30 June 2011 (a revised permit applies since the latter date), the competent authority has undertaken 36 enforcement visits, including nine site visits and audits, five air emission sampling and monitoring visits, and 22 water emission sampling and

monitoring visits. The Commission is of the view that the number of inspections is sufficient and it seems clear that the competent authority is closely monitoring the operation of the installation;

- Ireland confirms that the installation has not been subject to administrative fines over the past years;

- Ireland also confirms that there are no appeal procedures before the national courts in relation to the permitting of the installation, although there are civil proceedings before the High Court linked to the installation.

Based on the information provided by the Irish authorities, the Commission cannot identify any breach of Directive 2006/21/EC on the Management of Waste from Extractive Industries, nor of the IPPC Directive. In the light of the foregoing, the Commission proposed closing the complaint file at the end of October 2011. In response to a pre-closure letter, the complainant asked the Commission to clarify before it closes the enquiry, whether it is of the view that the waste in question is hazardous or not. The Commission is currently analysing this question.

7. Commission reply (REV. IV), received on 24 October 2012

The observations of the Commission

In its last communication, the Commission reported that, following an exchange with the Irish authorities, it could not identify any breach of either Directive 2006/21/EC on the Management of Waste from Extractive Industries, or of the IPPC Directive.

In response to the Commission's pre-closure letter, the complainant objected to closure and asked the Commission to clarify a number of points arising from Ireland's reply to the EU enquiry. Specifically, the complainant asked about the hazardous nature of the red mud waste. Secondly, he requested clarification as to whether the caustic content of the waste has indeed been removed, and the third question concerned the applicability of Directive 2006/21 on mining waste.

The Commission has now completed further analysis of these issues and has addressed additional questions to the Irish authorities. The Commission looked in particular at the information provided in the company's annual report, which was not part of the original information submitted, and concluded that the contents of the red mud waste pond at the Aughinish Alumina plant in Askeaton, County Limerick appear to be hazardous.
(http://www.epa.ie/licences/lic_eDMS/090151b2802a9459.pdf).

Under Point 27 of Annex IB to Council Directive 91/689/EC on hazardous waste, "Wastes which contain any of the constituents listed in Annex II and having any of the properties listed in Annex III and consisting of (…) liquids or sludges containing metals or metal compounds" shall be identified as hazardous waste. Point H8 of Annex III to the same directive mentions corrosiveness as a characteristic which renders waste hazardous and note 1 thereto indicates that "attribution of the hazardous properties 'toxic' (and 'very toxic'), 'harmful, 'corrosive' and

'irritant' is made on the basis of the criteria laid down by Annex VI, part I A and part II B of Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, labelling and packaging of dangerous substances in the version as amended by Council Directive 79/831/EEC."

Commission Directive 2001/159/EC adapting to technical progress for the 28th time Council Directive 67/548/EEC states that "a substance or preparation should also be considered corrosive if the result can be predicted, for example from strongly acid or alkaline reactions indicated by a pH of 2 or less or 11.5 or greater". Monitoring data included in Attachment 3 to the company's Annual Environmental Report (2008), show that pH values above 11.5 for the red mud were measured throughout 2008. Therefore, it appears that the red mud should have been classified as hazardous.

In this light, the Commission asked the Irish authorities to confirm that its conclusion that the waste is classified as hazardous is correct. It also asked for confirmation that the installation uses the so-called "dry storage" method for the disposal of the red mud, meaning that the caustic sodium hydroxide content is removed and it is only the solid fraction of the waste that is being landfilled.

On the basis of the above conclusion that the waste is hazardous, this means that Ireland has additional obligations under Directive 2006/21 on mining waste. This facility (storage of red mud) should be considered as a 'Category A' facility. This means that Ireland should have emergency plans in place in accordance with Article 6 of the directive, and these plans should be both internal and external.

Conclusion

In light of the above, the Commission has asked Ireland to inform it whether the site has been classified as a 'Category A' facility, and whether the appropriate internal and external plans have been drawn up and whether they are available.

8. Commission reply (REV. V), received on 29 September 2014

In its last communication, the Commission reported that it was seeking information from the Irish authorities on the nature of the red mud waste and the installations compliance with Directive 2006/21/EC[1] on the management of waste from extractive industries. The Commission services have now completed the assessment of these issues.

With regard to the compliance with Directive 2006/21/EC, the Irish authorities have confirmed that the Aughinish Alumina plant is currently regulated as an extractive waste facility in accordance with the Directive 2006/21/EC, and is regarded by the Irish Environmental Protection Agency (EPA) as a "Category A" facility and therefore subject to all relevant requirements of the Directive.

With regard to the requirements to put in place emergency plans, the Irish authorities have confirmed that the installation complies with Articles 5 and 6 of the Directive. In April 2013,

[1] OJ L 102 11.4.2006, p.15.

the licensee prepared and the EPA approved the Extractive Waste Management Plan for Aughinish Aluminia Ltd. The Internal and External Emergency Plans were also put in place in accordance with the Directive in 2013. The External Emergency Plan, following two rounds of public consultation, was prepared and adopted by Limerick County Council on 24 September 2013 and is publicly available at the County Council.

In his correspondence to the Commission services the petitioner has asked the Commission to investigate whether the installation complies with various conditions set out in the applicable licence in relation to the protection of soil, water, air, flora and fauna and human health. However, the petitioner has not substantiated any of his claims as to why the specific licence terms and conditions would not ensure compliance with Directive 2006/21/EC, in particular Articles 4 and 13, or that the licence conditions are not being complied with or enforced. Furthermore, the Irish authorities have informed the Commission services that the EPA is satisfied that the installation is compliant with its current IPPC licence. In the absence of evidence to the contrary, the Commission services are not in a position to challenge that assessment.

With regard to the method of disposal of red mud, the Irish authorities have confirmed that the Aughinish Alumina installation uses the dry storage method which involves the removal of liquid and sodium hydroxide from the initial red mud liquor produced. Some residual sodium hydroxide and moisture does remain in the final red mud that is sent for disposal on-site and these require on-going management by the licensee to ensure protection of the environment, including initial containment, dust control and neutralisation of leachate.

With regard to the waste characterisation at the Aughinish Aluminia site, following the initial assessment of the installation's annual reports provided to the Commission by the petitioner, the Commission services sought further clarifications from the Irish authorities. In their replies, the Irish authorities provided copies of laboratory analysis commissioned by the licensee and approved by the EPA for the purpose of determining the waste properties of red mud. The Commission assessed them and considers that the red mud deposited on-site is correctly characterised as non-hazardous according to the applicable EU legislation.

According to Article 2 of Decision 2000/532/EC[1] establishing a list of wastes, waste is classified as hazardous if it contains:

- one or more corrosive substances classified as R35 at a total concentration ≥ 1 %,
- one or more corrosive substances classified as R34 at a total concentration ≥ 5 %,
- one or more irritant substances classified as R41 at a total concentration ≥ 10 %,
- one or more irritant substances classified as R36, R37, R38 at a total concentration ≥ 20 %.

The information provided by the Irish authorities indicates that the red mud at this facility does not display the hazardous properties "corrosive" or "irritant".

With regard to the corrosive property, according to the EPA approved Extractive Waste Management Plan for Aughinish Aluminia Ltd, the total concentration of substances

[1] OJ L 226 6.9.2000, p.3.

classified as R35 ("causes severe burns") is 0.3%, which is below the relevant hazardous threshold of 1% as provided in the Decision 2000/532/EC. However, elevated pH values of above 11.5 are being observed for the red mud/leachate which is a potential trigger for a substance to be corrosive. This has also been brought to the attention of the Commission services by references to the licensee's Annual Environmental Reports[1]. The EPA has informed the Commission services about the results of in vitro skin corrosivity tests on red mud and its leachate commissioned by the licensee. These tests concluded that despite its elevated pH these wastes are not corrosive. Following the Irish authorities' agreement, copies of these test results were provided to the petitioner. The Commission services have also assessed the Extractive Waste Characterisation Report, which forms Appendix 2 of the Extractive Waste Management Plan, as approved by the EPA, and it shows that there are no substances contained within the red mud waste classified as R34 ("causes burns"). A copy of the Extractive Waste Management Plan was provided to the petitioner.

With regard to the irritant property, according to the EPA approved Extractive Waste Management Plan and Extractive waste Characterisation Report, the analysis of all the components of waste shows that the sum of the concentrations of the substances classified as R36 ("irritating to eyes"), R37 ("irritating to respiratory system") and R38 ("irritating to skin") is 7.1%, which is below the threshold of total concentration ≥ 20% established in Decision 2000/532/EC. Therefore, the waste is not to be classified as irritant. The EPA does not require to carry out specific tests if the percentage of substances within the waste with irritant risk phrases is below the relevant threshold of 20%. The EU legislation also does not require in this case the licensee to undergo further irritant property testing.

These assessments are based on reports carried out by the licensee and accepted by the EPA. The EPA is the competent authority to verify that the activity of the licensee complies with the national and EU law and the terms and conditions of the applicable license, including through the verification and approval of any reports from the licensee. The applicable licence sets specific terms and conditions in relation to control and monitoring. These provisions require the licensee to ensure that sampling, analyses, measurements, examinations, maintenance and calibrations are carried out by competent staff in accordance with documented operating procedures and the relevant safeguards on quality control. Where analysis is sub-contracted it shall be to a competent laboratory of the choice of the licensee. EU environmental law does not address the issue of whether the tests have to be carried out by the waste owner or the competent authority.

With regard to the method of testing, the test methods to be applied are those indicated in Directive 67/548/EC[2] on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances and in Directive 1999/45/EC[3] concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. It is to be noted that the assessment of the hazardous properties of waste can be done based on the constituents of the waste (i. e. the composition of waste, % of hazardous compounds therein) or by performing tests. In this case, the licensee assessed the

[1] The reports are available at: http://www.epa.ie

[2] OJ L 196 16.8.1967, p.1.
[3] OJ L 200 30.7.1999, p.1.

concentration levels of components for irritant properties and with regard to components with corrosive properties the licensee used tests. The Commission services are not in possession of information that would challenge the validity of the testing methods utilised in this particular case.

The petitioner was informed of this assessment by a letter of 23 August 2013. Further information received from the petitioner did not provide any new elements that would change the conclusions of that assessment or put in question the information provided by the competent national authorities. The Commission services closed the complaint file of the petitioner on 27 August 2014.

Therefore, following exchange with the petitioner and the Irish authorities within the framework of an EU pilot file, the Commission services have not identified a breach of EU environmental law regarding the operation of the installation concerned.

APPENDIX

C OECD TEST RESULTS FOR SKIN CORROSIVITY AND OCULAR IRRITATION

Together, a step forward for mankind.

Study N°20150160TCUC

Sample 1 Farmed red mud 2015

In Vitro Skin Corrosion: Human Skin Model Test (OCDE 431)

Baugy, February 22, 2016

SPONSOR:
Rusal Aughinish Alumina
Aughinish Alumina Limited
Aughinish Island
Askeaton
Co. Limerick
IRELAND

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GLP COMPLIANCE STATEMENT

Study number : 20150160TCUC

Study title : In Vitro Skin Corrosion: Human Skin Model Test
(OCDE 431)

The study took place in compliance with Annexe II a l'article D523-8 du code de l'Environnement, dated October 16, 2007, which is in accordance with the Directive 2004/10/EC.

Study Director :
A. Bouchard, Study Engineer

22 Feb 2016
Date

Signature

QUALITY ASSURANCE STATEMENT

Study Number: 20150160TCUC

Sample 1 Farmed red mud 2015: In Vitro Skin Corrosion Human Skin Model Test (OECD 431)

The study has been reviewed by the GLP Quality Assurance Unit of CERB and the report accurately reflects the raw data of the study.

Audits of this study were carried out on the following dates and reported to the Study Director (SD) and to the Management.

Study–based audits	Audit on	Forwarded to SD and Management
Study Plan	12 Nov 2015	12 Nov 2015
Experimental procedure	01, 03 and 04 Dec 2015	04 Dec 2015
Raw data and draft 1 report	19 and 20 Jan 2016	20 Jan 2016
Final check of report	15 Feb 2016	15 Feb 2016

Study-based/process-based and facility audits were performed in compliance with CERB procedures 9.02 and 9.13.

Mrs. S. Bidoli-Beutin
Quality Engineer
Responsible for Quality Assurance

23 Feb 2016
Date

Signature

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SUMMARY

The aim of the study was to assess the skin corrosion potential of Sample 1 Farmed red mud 2015 (batch No. Q1) using an *in vitro* skin corrosion model based on reconstructed human skin.

Firstly, a preliminary study was performed to identify the possible interference between MTT and test item. In a second phase, the main study involved 15 reconstructed epidermis units (3 per exposure time) as described below:

Table 1 Design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Negative control: sodium chloride solution at 0.9%; Positive control: potassium hydroxide solution at 8 mol/L

Test item and negative control were applied topically for 3 minutes and 1 hour and positive control was applied 3 minutes to a three-dimensional human skin model. After rinsing of tissues, assay medium was replaced by MTT-medium. Following 3 hours incubation, the formed blue formazan salt was extracted with isopropanol and the optical density was determined spectrophotometrically at 550 nm $\pm$ 10 nm. The optical density values obtained for each group were used to calculate the percentage of cell viability and consequently to classify the test item as corrosive or non-corrosive.

Results:
Preliminary study:
Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

Main study:
After 3 minutes of treatment, the positive control item showed a cell viability percentage of 16% (84% decrease). Consequently, the positive control item was classified as corrosive. This result validated the ongoing sensitivity of the method used.
After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was 100% for each exposure time.

Under the experimental conditions adopted, Sample 1 Farmed red mud 2015 (batch No. Q1) was classified as non-corrosive on the SkinEthic human reconstructed epidermis.

PART I
EXPERIMENTAL STUDY PLAN

1.1 AIM

The aim of the study was to assess any skin corrosion potential of Sample 1 Farmed red mud 2015 with an *in vitro* model using human skin.

1.2 PRINCIPLE

The test item is applied topically to a three-dimensional human skin model, comprising at least a reconstructed epidermis with a fonctional stratum corneum. The principle of the human skin model assay is based on the hypothesis that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion, and are cytotoxic to the underlying cell layers.

Corrosive test items are identified by their ability to produce a decrease in cell viability below defined threshold levels at specified exposure periods. Viability is quantified by using MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide].

The precipitated blue formazan product is then extracted and the optical density is read with a spectrophotometric technique at 550 mm $\pm$ 10 nm.

1.3 GLP REGULATION REQUIREMENTS

The study took place in compliance with Annexe II à l′article D523-8 du code de l′Environnement, which are in accordance with the Directive 2004/10/EC.

Approval for the site of experimentation: No. C-18-023-01.

1.4 DEVIATIONS FROM STUDY PLAN

1.4.1 MAJOR DEVIATIONS

There was no major deviation during the course of the study.

1.4.2 MINOR DEVIATIONS

Deviation n°1 in *Presentation and analysis of results*, Section 1.11, page 16: The optical density value for the negative control at time 3 minutes was read on 15 points instead of 9 to express the results of the positive control group only.
Reason: Technician error during the extraction procedure without impact on the results of the study.

With the exception of the point reported and justified above, the study took place in accordance with the study plan.

1.5 STUDY DATES

- Start of the study (signature of the study plan by the Study Director): 16 Nov 2015
- Start of the experimental period: 03 Dec 2015
- End of the experimental period: 04 Dec 2015
- End of the study at the signature of this report by the Study Director

1.6 DIRECTIVE COMPLIANCE STATEMENT

A skin-corrosion potential of test item is evaluated in a three-dimensional human skin model. The method is based on the general requirements of OECD Guideline No. 431 (April 13, 2004) and subsequent amendments, the NIH Publication No. 04-4510 dated on May 2004 and the European Chemicals Bureau, Method B40 - Skin Corrosion.

1.7 INITIAL CONSIDERATIONS

Validation studies have reported that tests employing human skin models are able to reliably discriminate between known skin corrosives and non-corrosives.

The test described in this Guideline allows the identification of corrosive chemical substances and mixtures. It further enables the identification of non-corrosive substances and mixtures when supported by a weight of evidence determination using other existing information (e.g., pH, structure-activity relationships, human and/or animal data). It does not normally provide adequate information on skin irritation, nor does it allow the subcategorisation of corrosive substances as permitted in the Globally Harmonised Classification System (GHS).

For a full evaluation of local skin effects after single dermal exposure, it is recommended to follow the sequential testing strategy as appended to Test Guideline 404 (2) and provided in the Globally Harmonised System. This testing strategy included the conduct of *in vitro* tests for skin corrosion (as described in this guideline) and skin irritation before considering testing in live animals.

1.8 TEST ITEM, CONTROL ITEMS, REFERENCE ITEM AND VEHICLE INFORMATION

1.8.1 Test item

Name: Sample 1 Farmed red mud 2015
Supplier: Rusal Aughinish Alumina
Batch Number: Q1
Galenic form: mud
Purity: conform to the CoA information
Weighing correction factor: none
Expiry date: Nov 2016
Intended use: chemicals

On 15 Oct 2015, 50 g was received in vial labelled "SAMPLE 1 FormED RED MUD, batch No. 2015" and also referred as "SAMPLE 1 Farmed RED MUD, batch No. 2015" on the certificate of analysis.

The study monitor confirmed that this test item corresponds to Sample 1 Farmed red mud 2015, batch No. Q1, name used throughout the study report.

Storage conditions: Immediately upon receipt, the test item was registered, then stored at room temperature in accordance with the Sponsor′s instructions. The complete description of the chemical and physical properties of the test item including stability is the responsibility of the Sponsor.

Handling instructions for test item: General safety procedures as appropriate for handling of chemicals of unknown hazard potential were applied.

Incompatibility: No known or suspected incompatibilities of the test item with any material likely to come in contact with it during the course of the study were specified by the Sponsor.

Remaining test item: After the issue of the first draft report, the Study Monitor confirmed that the remaining test item, except the sample to be archived, will be returned to the Sponsor.

The certificate of analysis of test item is presented in Appendix A, page 25.

1.8.2 Positive control item

Potassium hydroxide solution at 8 mol/l was used as positive control item.

1.8.3 Negative control item

Sodium chloride solution at 0.9% was used as negative control item.

1.8.4 Vehicle

Not used in the study.

1.8.5 Reference item

Not applicable for this kind of study.

1.8.6 Application of the test and control items

39.7 μl of the negative control item or the positive control item was applied to uniformly cover the skin surface.

19.8 mg of test item was applied to cover the skin and was moistened with 19.8μL of sodium chloride solution (0.9%) to ensure good contact with the skin. The test item was ground to a powder before application. At the end of the exposure period, the test material was carefully washed from the skin surface with phosphate buffer solution (PBS+).

1.9 MATERIAL

1.9.1 Human skin models

Reference: RHE/S/17.
The certificate of analysis is included in Appendix B, page 27.

Origin: SkinEthic Laboratories - 4 rue Alexander Fleming - 69007 Lyon - France.

Age: 17 days at the start of the experiment.

Number: The study involved 15 units of reconstructed epidermis.

- Test item: 3 tissue replicates were used for each exposure time (*i.e.*, 3 minutes and 1 h)
- Positive control group: 3 tissue replicates were used for each exposure time of 3 minutes.
- Negative control group: 3 tissue replicates were used for each exposure time (*i.e.*, 3 minutes and 1 h).

1.9.2 Apparatus

- Spectrophotometer MRXe, DYNEX TECHNOLOGY MAGELLAN BIOSCIENCES
- Laminar flow hood

1.9.3 Reagents

- Reconstructed Human Epidermis, SkinEthic Laboratories, Batch No. 15-RHE-145, Expiry date: 07 Dec 2015
- Maintenance Medium, SkinEthic Laboratories, Batch No. 15 MA 091, Expiry date: 14 Dec 2015
- MTT [3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide] SIGMA, Ref No. M5665, Batch No. MKBV3098V, Expiry date: Nov 2020
- Sodium chloride solution, Cooper, Batch No. 201264, Expiry date: Apr 2018
- Potassium hydroxide solution, SIGMA, Ref No. P5958, Batch No. S2BF153AV, Expiry date: Nov 2020
- Phosphate buffer saline solution (PBS+), Invitrogen/Gibco, Ref No. 14040-091, Batch No. 1708205, Expiry date: Jul 2018

1.10 EXPERIMENTAL PROTOCOL

1.10.1 Study design

Preliminary study:
Since the test item could interfere with the MTT endpoint, a preliminary study was performed.
This preliminary study was performed in one step.
Step 1 : to identify the possible interference, test item was checked for its ability to reduce MTT

directly. As the test item in contact with the MTT solution did not turn blue/purple, the test item did not interfere with the MTT, then the step No. 2 was not done.

Main study:
The study involved 3 groups of 3 reconstructed epidermis units per exposure time (see Table 1.1, page 15).

Table 1.1 Study design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Reliability check: A positive control group of 3 reconstructed epidermis units was tested in parallel to validate the ongoing sensitivity of the method used. This confirms that potassium hydroxide, a test item recognised as being corrosive, continues fully to exert its corrosive properties under the experimental conditions employed.

Justification of the number of reconstructed epidermis per group: The number of reconstructed epidermis per group is the minimum number enabling an accurate assessment of the studied effect according to the General Requirements of OECD Guideline No. 431 (April 13, 2004).

1.10.2 Choice of doses

The test item was tested as ready-to-use.

1.10.3 Dose adjustment

As test item was used undiluted, no concentration adjustement was done.

1.10.4 Test procedure

Test item, negative control and positive control were applied topically to a three-dimensional human skin model, comprising a reconstructed epidermis with a functional stratum corneum.

The test was performed as follows:

- Tissues were conditioned by pre-incubation for 43 hours 44 minutes.
- Tissues were transferred to fresh maintenance medium and topically exposed with the test chemicals (19.8 mg + 19.8 μL of 0.9% NaCl), or negative and positive control (39.7μL) for 3 minutes and/or 1 hour.
- After exposure tissues were rinsed and blotted. Assay medium was replaced by MTT-medium.

- After 3 hours incubation, tissues were washed with phosphate buffer saline solution and the blue formazan salt was extracted with isopropanol. The optical density of the formazan extract was determined spectrophotometrically at 550nm ± 10 nm.

1.11 PRESENTATION AND ANALYSIS OF RESULTS

1.11.1 Presentation of results

Cell viability was calculated for each tissue as % of the mean of the negative control tissue. Skin corrosivity potential of test item is classified according to the remaining cell viability obtained after 3 minutes and / or 1 hour exposure.
The optical density (OD) values and calculated percentage cell viability data for the test item, the positive and the negative controls were reported in tabular form including mean values.

1.11.2 Analysis of results

The optical density (OD) values obtained for each test item were used to calculate percentage viability relative to the negative control, which is arbitrarily set at 100%. Test item was classified as corrosive or non-corrosive on the basis of the results obtained in accordance with OECD Guideline No. 431 (April 13, 2004) and subsequent amendments Table 1.2, page 16.

Table 1.2 Prediction of corrosivity

Classification	Criteria for In Vitro interpretation
Corrosive	If viability <50% after 3 min exposure or If viability ≥50% after 3 min exposure and <15% after 1 hour
Non-corrosive	If viability ≥50% after 3 min exposure and ≥15% after 1 hour

1.11.3 Data recording

Both qualitative and quantitative individual data were collected using RS/1 software (release 6.3, APPLIED MATERIALS).

1.12 QUALITY ASSURANCE

The Quality Assurance Unit confirmed that operating procedures governing studies were strictly applied, by periodic in-study audits. These audits were undertaken at random over the course of the year according to CERB internal SOPs. The experimental report in English and data were audited by Quality Assurance Unit, in accordance with the standard procedures of the Centre.

1.13 ARCHIVES

1.13.1 Archives of records

The study plan, raw data, correspondence and the report will be stored for 10 years at CERB - 18800 Baugy, France, starting from the date of the final report. Quality Assurance reports will be stored at the Testing Facility without time limit.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- continued storage of records
- return of records to the Sponsor
- destruction of records

1.13.2 Archives of test item

One sample of the test item (1 g approximately) at the end of the study will be stored for 10 years at CERB - 18800 Baugy - France, starting from the date of the final report.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- return of sample to the Sponsor
- destruction of sample

PART II
EXPERIMENTAL RESULTS

2.1 REPORT OF RESULTS

2.1.1 Preliminary study

Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

2.1.2 Main study

Mean and individual values are presented on page 21.

After 3 minutes of treatment, the positive control item showed a decrease in cell viability percentage of -84% when compared with the negative control, which is arbitrarily set at 100%.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was similar to that of the negative control group, in both cases (*i.e.* +21% and +5%, respectively).

2.2 DISCUSSION

As the positive control item after 3 minutes of treatment showed a decrease in cell viability percentage of -84% when compared with the the negative control, the calculated cell viability percentage was 16%.
As the positive control group showed a cell viability value less than 50%, it was classified as corrosive as expected and according to the OECD Guideline No.431. This result validated the ongoing sensitivity of the method used.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was close to 100% in both cases (*i.e.* +21% and +5% respectively). This scale of variation is minor and and can be attributed to inter-individual variation of reconstructed epidermis. Since the test item was not presumed to interfere with the MTT endpoint (*i.e.* preliminary study), the cell viability was set at 100% in both cases.

After 3 minutes and 1 hour of treatment with the undiluted test item, as cell viability values were more than 50% and more than 15% respectively, the test item was classified as non-corrosive.

Results are summarised in Table 2.1, page 20:

Table 2.1 Cell viability and prediction of corrosivity

Treatment	Viability (%) T=3 min	Viability (%) T=1 hour	Classification
Negative control (NaCl 0.9%)	100	100	Non-corrosive
Test item	100	100	Non-corrosive
Positive control (KOH 8 mol/L)	16	/	Corrosive

Test item: Sample 1 Farmed red mud 2015
Cell viability is calculated for each tissue as % of the mean of the negative control tissue.
Electronic authentication: approved by Armelle Bouchard on 18-DEC-2015 at 14:57:22.407
Study 20150160TCUC

2.3 CONCLUSION

Under the experimental conditions adopted, Sample 1 Farmed red mud 2015 (batch No. Q1) was classified as non-corrosive on the SkinEthic human reconstructed epidermis.

OPTICAL DENSITY: INDIVIDUAL AND MEAN VALUES

Table 2.2 Optical density - Positive control (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.409	1.183
	SEM	0.029	0.034
	N	15	9
Positive control	Mean	0.222	NA
	SEM	0.014	NA
	N	9	0
	%	-84	NA

No statistical analysis.
NA: not applicable
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 16:51:57.329
Study 20150160TCUC

Table 2.3 Optical density - Positive control (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
	E6	1.579	NE
	F6	1.223	NE
	E7	1.454	NE
	F7	1.464	NE
	E8	1.514	NE
	F8	1.516	NE
Positive control	E9	0.282	NE
	F9	0.276	NE
	G9	0.256	NE
	E10	0.183	NE
	F10	0.183	NE
	G10	0.172	NE
	E11	0.226	NE
	F11	0.212	NE
	G11	0.208	NE

NE: not evaluated
Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 16:51:57.329
Study 20150160TCUC

Table 2.4 Optical density (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.376	1.183
	SEM	0.032	0.034
	N	9	9
Sample 1 Farmed red mud 2015	Mean	1.671	1.242
	SEM	0.035	0.029
	N	9	9
	%	+21	+5

No statistical analysis.
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 16:39:24.181
Study 20150160TCUC

Table 2.5 Optical density (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
Sample 1 Farmed red mud 2015	B6	1.528	1.129
	C6	1.536	1.175
	D6	1.593	1.192
	B7	1.669	1.167
	C7	1.637	1.243
	D7	1.709	1.245
	B8	1.783	1.293
	C8	1.786	1.349
	D8	1.796	1.385

Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 16:39:24.181
Study 20150160TCUC

APPENDICES

Appendix A

CERTIFICATE OF ANALYSIS OF TEST ITEM

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CERB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

Aughinish Alumina Limited, Aughinish Island, Askeaton, Co Limerick, V94 V8F7 – Ireland
Tel. +353 (0)61 604000 – Fax +353(0)61 604242 – www.rusal.com
DIRECTORS: K Bezzubov, R Bogaudinov, D A Clancy, S Garland, D Goldberg, O Stasev, K Strunnikov, Y Sukhanova
Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

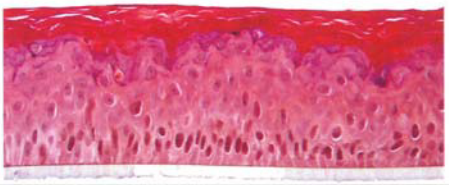
Appendix B

CERTIFICATE OF ANALYSIS OF RECONSTRUCTED EPIDERMIS

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS
RECONSTRUCTED HUMAN EPIDERMIS

CCE-093-RHE D17-S/01

Description:	**Reconstructed Human Epidermis (RHE/S/17)**		
	0.5 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on inert polycarbonate filters in chemically defined medium, for 17 days.		
Usage:	**FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN**		
Storage:	This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO_2 with saturated humidity.		
Passage:	Second (strain n° PK2 PKP.E-12)		
Batch N°:	**15-RHE-145**		
Origin:	Foreskin		
Histology:	 **Control n° E152173**		
Quality Controls:	**Test**	**Specification**	**Result**
	Histological observation (HES stained vertical paraffin sections, n=5)	Number of cell layers ≥ 4 Absence of significant histological abnormalities	**6 cell layers** Absence of significant histological abnormalities
		Well differentiated epidermis consisting of basal, spinous, granular layers and a stratum corneum	Satisfactory
	Cell viability (570 nm optical density, MTT test, n=2)	O.D. > 0.7	**O.D. = 1.1** (CV = 2.2 %)
	Barrier function integrity test (Exposure Time inducing 50% viability using Triton X-100 1%, n =12)	4.0h ≤ ET50 ≤ 10.0h	**5.4** h
Biological safety:	On blood of the same donor, we have verified: . the absence of HIV1 and 2 antibodies . the absence of hepatitis C antibodies . the absence of hepatitis B antigen HBs On epidermal cells of the same donor, we have verified: . the absence of mycoplasma		
Expiration date	December 7, 2015.		

"The use of this human tissue is strictly limited to in vitro testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited"

Lyon, December 1, 2015.
Certified and released by
Julie BIDOGGIA, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

Study N°20150161TCUC

Sample 2 Farmed red mud 2015

In Vitro Skin Corrosion: Human Skin Model Test (OCDE 431)

Baugy, February 22, 2016

SPONSOR:
Rusal Aughinish Alumina
Aughinish Alumina Limited
Aughinish Island
Askeaton
Co. Limerick
IRELAND

TESTING FACILITY:
Centre de Recherches Biologiques (CERB)
Chemin de Montifault
18800 Baugy
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TESTING FACILITY'S APPROVAL

Testing Facility Management:
S. Richard, Pharm.D, Ph.D
European Registered Toxicologist
Email: serge.richard@cerb.fr

23 Feb 2016
Date

Signature

Safety Assessment Director:
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23. Feb. 2016
Date

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22 Feb 2016
Date

Signature

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On behalf of the Sponsor:
Mrs L. Clune
Study Monitor
Rusal Aughinish Alumina
Aughinish Alumina Limited
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Email: louise.clune@augh.com

GLP COMPLIANCE STATEMENT

Study number : 20150161TCUC

Study title : In Vitro Skin Corrosion: Human Skin Model Test (OCDE 431)

The study took place in compliance with Annexe II a l'article D523-8 du code de l'Environnement, which are in accordance with the Directive 2004/10/EC.

Study Director :
A. Bouchard, Study Engineer

22 Feb 2016
Date

Signature

QUALITY ASSURANCE STATEMENT

Study Number: 20150161TCUC

Sample 2 Farmed red mud 2015: In Vitro Skin Corrosion Human Skin Model Test (OECD 431)

The study has been reviewed by the GLP Quality Assurance Unit of CERB and the report accurately reflects the raw data of the study.

Audits of this study were carried out on the following dates and reported to the Study Director (SD) and to the Management.

Study–based audits	**Audit on**	**Forwarded to SD and Management**
Study Plan	12 Nov 2015	12 Nov 2015
Experimental procedure	01, 03 and 04 Dec 2015	04 Dec 2015
Raw data and draft 1 report	19 and 20 Jan 2016	20 Jan 2016
Final check of report	15 Feb 2016	15 Feb 2016

Study-based/process-based and facility audits were performed in compliance with CERB procedures 9.02 and 9.13.

Mrs. S. Bidoli-Beutin
Quality Engineer
Responsible for Quality Assurance

Date _____ Signature _____

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SUMMARY

The aim of the study was to assess the skin corrosion potential of Sample 2 Farmed red mud 2015 (batch No. Q2) using an *in vitro* skin corrosion model based on reconstructed human skin.

Firstly, a preliminary study was performed to identify the possible interference between MTT and test item. In a second phase, the main study involved 15 reconstructed epidermis units (3 per exposure time) as described below:

Table 1 Design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Negative control: sodium chloride solution at 0.9%; Positive control: potassium hydroxide solution at 8 mol/L

Test item and negative control were applied topically for 3 minutes and 1 hour and positive control was applied 3 minutes to a three-dimensional human skin model. After rinsing of tissues, assay medium was replaced by MTT-medium. Following 3 hours incubation, the formed blue formazan salt was extracted with isopropanol and the optical density was determined spectrophotometrically at 550 nm $\pm$ 10 nm. The optical density values obtained for each group were used to calculate the percentage of cell viability and consequently to classify the test item as corrosive or non-corrosive.

Results:
Preliminary study:
Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

Main study:
After 3 minutes of treatment, the positive control item showed a cell viability percentage 16%. As expected and according to the OECD Guideline No.431, the positive control item was classified as corrosive. This result validated the ongoing sensitivity of the method used.
After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was 100% for each exposure time.

Under the experimental conditions adopted, Sample 2 Farmed red mud 2015 (batch No. Q2) was classified as non-corrosive on the SkinEthic human reconstructed epidermis.

PART I
EXPERIMENTAL STUDY PLAN

1.1 AIM

The aim of the study was to assess any skin corrosion potential of Sample 2 Farmed red mud 2015 with an *in vitro* model using human skin.

1.2 PRINCIPLE

The test item is applied topically to a three-dimensional human skin model, comprising at least a reconstructed epidermis with a functional stratum corneum. The principle of the human skin model assay is based on the hypothesis that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion, and are cytotoxic to the underlying cell layers.

Corrosive test items are identified by their ability to produce a decrease in cell viability below defined threshold levels at specified exposure periods. Viability is quantified by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide].

The precipitated blue formazan product is then extracted and the optical density is read with a spectrophotometric technique at 550 mm $\pm$ 10 nm.

1.3 GLP REGULATION REQUIREMENTS

The study took place in compliance with Annexe II à l′article D523-8 du code de l′Environnement, which are in accordance with the Directive 2004/10/EC.

Approval for the site of experimentation: No. C-18-023-01.

1.4 DEVIATIONS FROM STUDY PLAN

1.4.1 MAJOR DEVIATIONS

There was no major deviation during the course of the study.

1.4.2 MINOR DEVIATIONS

Deviation n°1 in *Application of the test and control items*, Subsection 1.8.6, page 13: Test item was not ground to a powder before application as initially mentioned in the study plan.
Reason: Since the test item showed a change of appearance after grinding and since it was possible to apply it on the skin surface as supplied, the test item was tested as provided.

Deviation n°2 in *Presentation and analysis of results*, Section 1.11, page 16: The optical density value for the negative control at time 3 minutes was read on 15 points instead of 9 to express the results of the positive control group only.
Reason: Technician error during the extraction procedure without impact on the results of the study.

With the exception of the point reported and justified above, the study took place in accordance with the study plan.

1.5 STUDY DATES

- Start of the study (signature of the study plan by the Study Director): 16 Nov 2015
- Start of the experimental period: 03 Dec 2015
- End of the experimental period: 04 dec 2015
- End of the study at the signature of this report by the Study Director

1.6 DIRECTIVE COMPLIANCE STATEMENT

A skin-corrosion potential of test item is evaluated in a three-dimensional human skin model. The method is based on the general requirements of OECD Guideline No. 431 (April 13, 2004) and subsequent amendments, the NIH Publication No. 04-4510 dated on May 2004 and the European Chemicals Bureau, Method B40 - Skin Corrosion.

1.7 INITIAL CONSIDERATIONS

Validation studies have reported that tests employing human skin models are able to reliably discriminate between known skin corrosives and non-corrosives. The test protocol may also provide an indication of the distinction between severe and less severe skin corrosives.

The test described in this Guideline allows the identification of corrosive chemical substances and mixtures. It further enables the identification of non-corrosive substances and mixtures when supported by a weight of evidence determination using other existing information (e.g., pH, structure-activity relationships, human and/or animal data). It does not normally provide adequate information on skin irritation, nor does it allow the subcategorisation of corrosive substances as permitted in the Globally Harmonised Classification System (GHS).

For a full evaluation of local skin effects after single dermal exposure, it is recommended to follow the sequential testing strategy as appended to Test Guideline 404 (2) and provided in the Globally Harmonised System. This testing strategy included the conduct of *in vitro* tests for skin corrosion (as described in this guideline) and skin irritation before considering testing in live animals.

1.8 TEST ITEM, CONTROL ITEMS, REFERENCE ITEM AND VEHICLE INFORMATION

1.8.1 Test item

Name: Sample 2 Farmed red mud 2015
Supplier: Rusal Aughinish Alumina
Batch Number: Q2
Galenic form: mud
Purity: conform to CoA information
Weighing correction factor: none
Expiry date: Nov 2016
Intended use: chemicals

On 15 Oct 2015, 50 g was received in vial labelled "SAMPLE 2 FormED RED Mud, batch No. 2015" and also referred as "SAMPLE 2 Farmed RED MUD, batch No. 2015" on the certificate of analysis. The study monitor confirmed that this test item corresponds to Sample 2 Farmed red mud 2015, batch No. Q2, name used throughout the study report.

Storage conditions: Immediately upon receipt, the test item was registered, then stored at room temperature in accordance with the Sponsor′s instructions. The complete description of the chemical and physical properties of the test item including stability is the responsibility of the Sponsor.

Handling instructions for test item: General safety procedures as appropriate for handling of chemicals of unknown hazard potential were applied. For further details about safety, the material safety data sheet was supplied with the test item by the Sponsor.

Incompatibility: No known or suspected incompatibilities of the test item with any material likely to come in contact with it during the course of the study were specified by the Sponsor.

Remaining test item: After the issue of the first draft report, the Study Monitor confirmed that the remaining test item, except the sample to be archived, will be returned to the Sponsor.

The certificate of analysis of test item is presented in Appendix A, page 25.

1.8.2 Positive control item

Potassium hydroxide solution at 8 mol/l was used as positive control item.

1.8.3 Negative control item

Sodium chloride solution at 0.9% was used as negative control item.

1.8.4 Vehicle

Not used in the study.

1.8.5 Reference item

Not applicable for this kind of study.

1.8.6 Application of the test and control items

39.7 μl of the negative control item and positive control item was applied to uniformly cover the skin surface.

19.8 mg of test item was applied to cover the skin and was moistened with sodium chloride solution (0.9%) to ensure good contact with the skin. Test item was not ground to a powder before application (see Section 1.4, page 11). At the end of the exposure period, the test material was carefully washed from the skin surface with phosphate buffer solution (PBS+).

1.9 MATERIAL

1.9.1 Human skin models

Reference: RHE/S/17.

Origin: SkinEthic Laboratories - 4 rue Alexander Fleming - 69007 Lyon - France.

Age: generally 17 days at the start of the experiment.

Number: The study involved 15 units of reconstructed epidermis.

- Test item: 3 tissue replicates were used for each exposure time (*i.e.*, 3 minutes and 1 h)
- Positive control group: 3 tissue replicates were used for each exposure time of 3 minutes
- Negative control group: 3 tissue replicates were used for each exposure time (*i.e.*, 3 minutes and 1 h)

1.9.2 Apparatus

- Spectrophotometer MRXe, DYNEX TECHNOLOGY MAGELLAN BIOSCIENCES
- Laminar flow hood

1.9.3 Reagents

- Reconstructed Human Epidermis, SkinEthic Laboratories, Batch No. 15-RHE-145, Expiry date: 07 Dec 2015
- Maintenance Medium, SkinEthic Laboratories, Batch No. 15 MA 091, Expiry date: 14 Dec 2015
- MTT [3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide] SIGMA, Ref No. M5665, Batch No. MKBV3098V, Expiry date: Nov 2020
- Sodium chloride solution, Cooper, Batch No. 201264, Expiry date: Apr 2018
- Potassium hydroxide solution, SIGMA, Ref No. P5958, Batch No. S2BF153AV, Expiry date: Nov 2020
- Phosphate buffer saline solution (PBS+), Invitrogen/Gibco, Ref No. 14040-091, Batch No. 1708205, Expiry date: Jul 2018

1.10 EXPERIMENTAL PROTOCOL

1.10.1 Study design

Preliminary study:
Since the test item could interfere with the MTT endpoint, a preliminary study was performed. This preliminary study was performed in one step.
Step 1 : to identify the possible interference, test item was checked for its ability to reduce MTT directly. As the test item in contact with the MTT solution did not turn blue/purple, the test item did

not interfere with the MTT, then the step No. 2 was not done.

Main study:
The study involved 3 groups of 3 reconstructed epidermis units per exposure time (see Table 1.1, page 15).

Table 1.1 Study design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Reliability check: A positive control group of 3 reconstructed epidermis units was tested in parallel to validate the ongoing sensitivity of the method used. This confirmed that potassium hydroxide, a test item recognised as being corrosive, continues fully to exert its corrosive properties under the experimental conditions employed.

Justification of the number of reconstructed epidermis per group: The number of reconstructed epidermis per group is the minimum number enabling an accurate assessment of the studied effect according to the General Requirements of OECD Guideline No. 431 (April 13, 2004).

1.10.2 Choice of doses

The test item was tested as ready-to-use.

1.10.3 Dose adjustment

As test item was used undiluted, no concentration adjustement was done.

1.10.4 Test procedure

Test item, negative control and positive control were applied topically to a three-dimensional human skin model, comprising a reconstructed epidermis with a functional stratum corneum.

The test was performed as follows:

- Tissues were conditioned by pre-incubation for 43 hours 44 minutes.
- Tissues were transferred to fresh maintenance medium and topically exposed with the test chemical (19.8 mg + 19.8 μL of 0.9% NaCl), or negative and positive control (39.7μL) for 3 minutes and/or 1 hour.
- After exposure tissues were rinsed and blotted. Assay medium was replaced by MTT-medium.

- After 3 hours incubation, tissues were washed with phosphate buffer saline solution and the blue formazan salt was extracted with isopropanol. The optical density of the formazan extract was determined spectrophotometrically at 550nm ± 10 nm.

1.11 PRESENTATION AND ANALYSIS OF RESULTS

1.11.1 Presentation of results

Cell viability was calculated for each tissue as % of the mean of the negative control tissue. Skin corrosivity potential of test item is classified according to the remaining cell viability obtained after 3 minutes and / or 1 hour exposure.
The optical density (OD) values and calculated percentage cell viability data for the test item, the positive and the negative controls were reported in tabular form including mean values.

1.11.2 Analysis of results

The optical density (OD) values obtained for each test item were used to calculate percentage viability relative to the negative control, which is arbitrarily set at 100%. Test item was classified as corrosive or non-corrosive on the basis of the results obtained in accordance with OECD Guideline No. 431 (April 13, 2004) and subsequent amendments Table 1.2, page 16.

Table 1.2 Prediction of corrosivity

Classification	Criteria for In Vitro interpretation
Corrosive	If viability <50% after 3 min exposure or If viability ≥50% after 3 min exposure and <15% after 1 hour
Non-corrosive	If viability ≥50% after 3 min exposure and ≥15% after 1 hour

1.11.3 Data recording

Both qualitative and quantitative individual data were collected using RS/1 software (release 6.3, APPLIED MATERIALS).

1.12 QUALITY ASSURANCE

The Quality Assurance Unit confirmed that operating procedures governing studies were strictly applied, by periodic in-study audits. These audits were undertaken at random over the course of the year according to CERB internal SOPs. The experimental report in English and data were audited by Quality Assurance Unit, in accordance with the standard procedures of the Centre.

1.13 ARCHIVES

1.13.1 Archives of records

The study plan, raw data, correspondence and the report will be stored for 10 years at CERB - 18800 Baugy, France, starting from the date of the final report. Quality Assurance reports will be stored at the Testing Facility without time limit.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- continued storage of records
- return of records to the Sponsor
- destruction of records

1.13.2 Archives of test item

One sample of the test item (1 g approximately) at the end of the study or at the end of the package of studies will be stored for 10 years at CERB - 18800 Baugy - France, starting from the date of the final report.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- return of sample to the Sponsor
- destruction of sample

PART II
EXPERIMENTAL RESULTS

2.1 REPORT OF RESULTS

2.1.1 Preliminary study

Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

2.1.2 Main study

Mean and individual values are presented on page 21.

After 3 minutes of treatment, the positive control item showed a decrease in cell viability percentage of -84% when compared with the negative control, which is arbitrarily set at 100%.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was similar to that of the negative control group, in both cases (*i.e.* +14% and +20%, respectively).

2.2 DISCUSSION

As the positive control item after 3 minutes of treatment showed a decrease in cell viability percentage of -84% when compared with the the negative control, the calculated cell viability percentage was 16%.
As the positive control group showed a cell viability value less than 50%, it was classified as corrosive as expected and according to the OECD Guideline No.431. This result validated the ongoing sensitivity of the method used.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was close to 100% in both cases (*i.e.* +14% and +20% respectively). This scale of variation is minor and and can be attributed to inter-individual variation of reconstructed epidermis. Since the test item was not presumed to interfere with the MTT endpoint (*i.e.* preliminary study), the cell viability was set at 100% in both cases.

After 3 minutes and 1 hour of treatment with the undiluted test item, as cell viability values were more than 50% and more than 15% respectively, the test item was classified as non-corrosive.

Results are summarised in Table 2.1, page 20:

Table 2.1 Cell viability and prediction of corrosivity

Treatment	Viability (%) T=3 min	Viability (%) T=1 hour	Classification
Negative control (NaCl 0.9%)	100	100	Non-corrosive
Test item	100	100	Non-corrosive
Positive control (KOH 8 mol/L)	16	/	Corrosive

Test item: Sample 2 Farmed red mud 2015
Cell viability is calculated for each tissue as % of the mean of the negative control tissue.
Electronic authentication: approved by Armelle Bouchard on 28-DEC-2015 at 18:22:43.352
Study 20150161TCUC

2.3 CONCLUSION

Under the experimental conditions adopted, Sample 2 Farmed red mud 2015 (batch No. Q2) was classified as non-corrosive on the SkinEthic human reconstructed epidermis.

OPTICAL DENSITY: INDIVIDUAL AND MEAN VALUES

Table 2.2 Optical density - Positive control (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.409	1.183
	SEM	0.029	0.034
	N	15	9
Positive control	Mean	0.222	NA
	SEM	0.014	NA
	N	9	0
	%	-84	NA

No statistical analysis.
NA: not applicable
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 17:48:39.658
Study 20150161TCUC

Table 2.3 Optical density - Positive control (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
	E6	1.579	NE
	F6	1.223	NE
	E7	1.454	NE
	F7	1.464	NE
	E8	1.514	NE
	F8	1.516	NE
Positive control	E9	0.282	NE
	F9	0.276	NE
	G9	0.256	NE
	E10	0.183	NE
	F10	0.183	NE
	G10	0.172	NE
	E11	0.226	NE
	F11	0.212	NE
	G11	0.208	NE

NE: not evaluated
Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 17:48:39.658
Study 20150161TCUC

Table 2.4 Optical density (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.376	1.183
	SEM	0.032	0.034
	N	9	9
Sample 2 Farmed red mud 2015	Mean	1.575	1.419
	SEM	0.026	0.026
	N	9	9
	%	+14	+20

No statistical analysis.
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 17:41:36.265
Study 20150161TCUC

Table 2.5 Optical density (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
Sample 2 Farmed red mud 2015	B9	1.659	1.449
	C9	1.640	1.517
	D9	1.702	1.513
	B10	1.528	1.320
	C10	1.532	1.419
	D10	1.583	1.486
	B11	1.461	1.309
	C11	1.530	1.353
	D11	1.542	1.406

Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 17:41:36.265
Study 20150161TCUC

APPENDICES

Appendix A

CERTIFICATE OF ANALYSIS OF TEST ITEM

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CERB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

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DIRECTORS: K Bezzubov, R Bogaudinov, D A Clancy, S Garland, D Goldberg, O Stasev, K Strunnikov, Y Sukhanova
Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

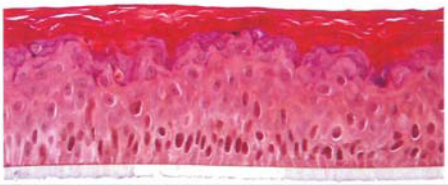
Appendix B

CERTIFICATE OF ANALYSIS OF RECONSTRUCTED EPIDERMIS

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS
RECONSTRUCTED HUMAN EPIDERMIS

CCE-093-RHE D17-S/01

Description:	**Reconstructed Human Epidermis (RHE/S/17)**		
	0.5 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on inert polycarbonate filters in chemically defined medium, for 17 days.		
Usage:	**FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN**		
Storage:	This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO_2 with saturated humidity.		
Passage:	Second (strain n° PK2 PKP.E-12)		
Batch N°:	**15-RHE-145**		
Origin:	Foreskin		
Histology:	 **Control n° E152173**		
Quality Controls:	**Test**	**Specification**	**Result**
	Histological observation (HES stained vertical paraffin sections, n=5)	Number of cell layers ≥ 4 Absence of significant histological abnormalities	**6 cell layers** Absence of significant histological abnormalities
		Well differentiated epidermis consisting of basal, spinous, granular layers and a stratum corneum	Satisfactory
	Cell viability (570 nm optical density, MTT test, n=2)	O.D. > 0.7	**O.D. = 1.1** (CV = 2.2 %)
	Barrier function integrity test (Exposure Time inducing 50% viability using Triton X-100 1%, n =12)	4.0h ≤ ET50 ≤ 10.0h	**5.4** h
Biological safety:	On blood of the same donor, we have verified: . the absence of HIV1 and 2 antibodies . the absence of hepatitis C antibodies . the absence of hepatitis B antigen HBs On epidermal cells of the same donor, we have verified: . the absence of mycoplasma		
Expiration date	December 7, 2015.		

"The use of this human tissue is strictly limited to in vitro testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited"

Lyon, December 1, 2015.
Certified and released by
Julie BIDOGGIA, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

Study N°20150162TCUC

Sample 3 Farmed red mud 2015

In Vitro Skin Corrosion: Human Skin Model Test (OCDE 431)

Baugy, February 22, 2016

SPONSOR:
Rusal Aughinish Alumina
Aughinish Alumina Limited
Aughinish Island
Askeaton
Co. Limerick
IRELAND

TESTING FACILITY:
Centre de Recherches Biologiques (CERB)
Chemin de Montifault
18800 Baugy
France

TESTING FACILITY'S APPROVAL

Testing Facility Management:
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Email: serge.richard@cerb.fr

23 Feb 2016
Date

Signature

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23. Feb. 2016
Date

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23 Feb 2016
Date

Signature

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SPONSOR

On behalf of the Sponsor:
Mrs L. Clune
Study Monitor
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Aughinish Alumina Limited
Aughinish Island
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Email: louise.clune@augh.com

GLP COMPLIANCE STATEMENT

Study number : 20150162TCUC

Study title : In Vitro Skin Corrosion: Human Skin Model Test (OCDE 431)

The study took place in compliance with Annexe II à l'article D523-8 du code de l'Environnement, which are in accordance with the Directive 2004/10/EC.

Study Director :
A. Bouchard, Study Engineer

22 Feb 2016
Date

Signature

QUALITY ASSURANCE STATEMENT

Study Number: 20150162TCUC

Sample 3 Farmed red mud 2015: In Vitro Skin Corrosion Human Skin Model Test (OECD 431)

The study has been reviewed by the GLP Quality Assurance Unit of CERB and the report accurately reflects the raw data of the study.

Audits of this study were carried out on the following dates and reported to the Study Director (SD) and to the Management.

Study–based audits	Audit on	Forwarded to SD and Management
Study Plan	12 Nov 2015	12 Nov 2015
Experimental procedure	01, 03 and 04 Dec 2015	04 Dec 2015
Raw data and draft 1 report	19 and 20 Jan 2016	20 Jan 2016
Final check of report	15 Feb 2016	15 Feb 2016

Study-based/process-based and facility audits were performed in compliance with CERB procedures 9.02 and 9.13.

Mrs. S. Bidoli-Beutin
Quality Engineer
Responsible for Quality Assurance 23 Feb 2016 (Date) (Signature)

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SUMMARY

The aim of the study was to assess the skin corrosion potential of Sample 3 Farmed red mud 2015 (batch No. Q3) using an *in vitro* skin corrosion model based on reconstructed human skin.

Firstly, a preliminary study was performed to identify the possible interference between MTT and test item. In a second phase, the main study involved 15 reconstructed epidermis units (3 per exposure time) as described below:

Table 1 Design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Negative control: sodium chloride solution at 0.9%; Positive control: potassium hydroxide solution at 8 mol/L

Test item and negative control were applied topically for 3 minutes and 1 hour and positive control was applied 3 minutes to a three-dimensional human skin model. After rinsing of tissues, assay medium was replaced by MTT-medium. Following 3 hours incubation, the formed blue formazan salt was extracted with isopropanol and the optical density was determined spectrophotometrically at 550 nm $\pm$ 10 nm. The optical density values obtained for each group were used to calculate the percentage of cell viability and consequently to classify the test item as corrosive or non-corrosive.

Results:
Preliminary study:
Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

Main study:
After 3 minutes of treatment, the positive control item showed a cell viability percentage of 16%. As expected and according to the OECD Guideline No.431, the positive control item was classified as corrosive. This result validated the ongoing sensitivity of the method used.
After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was 100% for each exposure time.

Under the experimental conditions adopted, Sample 3 Farmed red mud 2015 (batch No. Q3) was classified as <u>non-corrosive</u> on the SkinEthic human reconstructed epidermis.

PART I
EXPERIMENTAL STUDY PLAN

1.1 AIM

The aim of the study was to assess any skin corrosion potential of Sample 3 Farmed red mud 2015 with an *in vitro* model using human skin.

1.2 PRINCIPLE

The test item is applied topically to a three-dimensional human skin model, comprising at least a reconstructed epidermis with a functional stratum corneum. The principle of the human skin model assay is based on the hypothesis that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion, and are cytotoxic to the underlying cell layers.

Corrosive test items are identified by their ability to produce a decrease in cell viability below defined threshold levels at specified exposure periods. Viability is quantified by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide].

The precipitated blue formazan product is then extracted and the optical density is read with a spectrophotometric technique at 550 mm $\pm$ 10 nm.

1.3 GLP REGULATION REQUIREMENTS

The study took place in compliance with Annexe II à l′article D523-8 du code de l′Environnement, which are in accordance with the Directive 2004/10/EC.

Approval for the site of experimentation: No. C-18-023-01.

1.4 DEVIATIONS FROM STUDY PLAN

1.4.1 MAJOR DEVIATIONS

There was no major deviation during the course of the study.

1.4.2 MINOR DEVIATIONS

Deviation n°1 in *Application of the test and control items*, Subsection 1.8.6, page 13: Test item was not ground to a powder before application as initially mentioned in the study plan.
Reason: Since the test item showed a change of appearance after grinding and since it was possible to apply it on the skin surface as supplied, the test item was tested as provided.

Deviation n°2 in *Presentation and analysis of results*, Section 1.11, page 16: The optical density value for the negative control at time 3 minutes was read on 15 points instead of 9 to express the results of the positive control group only.
Reason: Technician error during the extraction procedure without impact on the results of the study.

With the exception of the point reported and justified above, the study took place in accordance with the study plan.

1.5 STUDY DATES

- Start of the study (signature of the study plan by the Study Director): 16 Nov 2015
- Start of the experimental period: 03 dec 2015
- End of the experimental period: 04 dec 2015
- End of the study at the signature of this report by the Study Director

1.6 DIRECTIVE COMPLIANCE STATEMENT

A skin-corrosion potential of test item is evaluated in a three-dimensional human skin model. The method is based on the general requirements of OECD Guideline No. 431 (April 13, 2004) and subsequent amendments, the NIH Publication No. 04-4510 dated on May 2004 and the European Chemicals Bureau, Method B40 - Skin Corrosion.

1.7 INITIAL CONSIDERATIONS

Validation studies have reported that tests employing human skin models are able to reliably discriminate between known skin corrosives and non-corrosives. The test protocol may also provide an indication of the distinction between severe and less severe skin corrosives.

The test described in this Guideline allows the identification of corrosive chemical substances and mixtures. It further enables the identification of non-corrosive substances and mixtures when supported by a weight of evidence determination using other existing information (e.g., pH, structure-activity relationships, human and/or animal data). It does not normally provide adequate information on skin irritation, nor does it allow the subcategorisation of corrosive substances as permitted in the Globally Harmonised Classification System (GHS).

For a full evaluation of local skin effects after single dermal exposure, it is recommended to follow the sequential testing strategy as appended to Test Guideline 404 (2) and provided in the Globally Harmonised System. This testing strategy included the conduct of *in vitro* tests for skin corrosion (as described in this guideline) and skin irritation before considering testing in live animals.

1.8 TEST ITEM, CONTROL ITEMS, REFERENCE ITEM AND VEHICLE INFORMATION

1.8.1 Test item

Name: Sample 3 Farmed red mud 2015
Supplier: Rusal Aughinish Alumina
Batch Number: Q3
Galenic form: mud
Purity: Conform to CoA information
Weighing correction factor: none
Expiry date: Nov 2016
Intended use: chemicals

On 15 Oct 2015, 50 g was received in vial labelled "SAMPLE 3 FormED RED mud, batch No. 2015" and also referred as "SAMPLE 3 Farmed RED MUD, batch No. 2015" on the certificate of analysis. The study monitor confirmed that this test item corresponds to Sample 3 Farmed red mud 2015, batch No. Q3, name used throughout the study report.

Storage conditions: Immediately upon receipt, the test item was registered, then stored at room temperature in accordance with the Sponsor′s instructions. The complete description of the chemical and physical properties of the test item including stability is the responsibility of the Sponsor.

Handling instructions for test item: General safety procedures as appropriate for handling of chemicals of unknown hazard potential were applied. For further details about safety, see the material safety data sheet supplied with the test item by the Sponsor.

Incompatibility: No known or suspected incompatibilities of the test item with any material likely to come in contact with it during the course of the study were specified by the Sponsor.

Remaining test item: After the issue of the first draft report, the Study Monitor confirmed that the remaining test item, except the sample to be archived, will be returned to the Sponsor.

The certificate of analysis of test item is presented in Appendix A, page 25.

1.8.2 Positive control item

Potassium hydroxide solution at 8 mol/l was used as positive control item.

1.8.3 Negative control item

Sodium chloride solution at 0.9% was used as negative control item.

1.8.4 Vehicle

Not used in the study.

1.8.5 Reference item

Not applicable for this kind of study.

1.8.6 Application of the test and control items

39.7 μl of the negative control item and positive control item was applied to uniformly cover the skin surface.

19.8 mg of test item was applied to cover the skin and was moistened with sodium chloride solution (0.9%) to ensure good contact with the skin. Test item was not ground to a powder before application (see Section 1.4, page 11). At the end of the exposure period, the test material was carefully washed from the skin surface with phosphate buffer solution (PBS+).

1.9 MATERIAL

1.9.1 Human skin models

Reference: RHE/S/17.

Origin: SkinEthic Laboratories - 4 rue Alexander Fleming - 69007 Lyon - France.

Age: 17 days at the start of the experiment.

Number: The study involved 15 units of reconstructed epidermis.

- Test item: 3 tissue replicates were used for each exposure time (*i.e.* 3 minutes and 1 h)
- Positive control group: 3 tissue replicates were used for each exposure time of 3 minutes.
- Negative control group: 3 tissue replicates were used for each exposure time (*i.e.* 3 minutes and 1 h).

1.9.2 Apparatus

- Spectrophotometer MRXe, DYNEX TECHNOLOGY MAGELLAN BIOSCIENCES
- Laminar flow hood

1.9.3 Reagents

- Reconstructed Human Epidermis, SkinEthic Laboratories, Batch No. 15-RHE-145, Expiry date: 07 Dec 2015
- Maintenance Medium, SkinEthic Laboratories, Batch No. 15 MA 091, Expiry date: 14 Dec 2015
- MTT [3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide] SIGMA, Ref No. M5665, Batch No. MKBV3098V, Expiry date: Nov 2020
- Sodium chloride solution, Cooper, Batch No. 201264, Expiry date: Apr 2018
- Potassium hydroxide solution, SIGMA, Ref No. P5958, Batch No. S2BF153AV, Expiry date: Nov 2020
- Phosphate buffer saline solution (PBS+), Invitrogen/Gibco, Ref No. 14040-091, Batch No. 1708205, Expiry date: Jul 2018

1.10 EXPERIMENTAL PROTOCOL

1.10.1 Study design

Preliminary study:
Since the test item could interfere with the MTT endpoint, a preliminary study was performed. This preliminary study was performed in one step.
Step 1 : to identify the possible interference, test item was checked for its ability to reduce MTT directly. As the test item in contact with the MTT solution did not turn blue/purple, the test item did

not interfere with the MTT, then the step No. 2 was not done.

Main study:
The study involved 3 groups of 3 reconstructed epidermis units per exposure time (see Table 1.1, page 15).

Table 1.1 Study design

Groups	Number of reconstructed epidermis units	Treatment	Tested concentration	Exposure time
1	3+3	Negative control	0.9%	3 minutes/1 hour
2	3+3	Test item	undiluted	3 minutes/1 hour
3	3	Positive control	undiluted	3 minutes

Reliability check: A positive control group of 3 reconstructed epidermis units was tested in parallel to validate the ongoing sensitivity of the method used. This confirmed that potassium hydroxide, a test item recognised as being corrosive, continues fully to exert its corrosive properties under the experimental conditions employed.

Justification of the number of reconstructed epidermis per group: The number of reconstructed epidermis per group is the minimum number enabling an accurate assessment of the studied effect according to the General Requirements of OECD Guideline No. 431 (April 13, 2004).

1.10.2 Choice of doses

The test item was tested as ready-to-use.

1.10.3 Dose adjustment

As test item was used undiluted, no concentration adjustement was done.

1.10.4 Test procedure

Test item, negative control and positive control were applied topically to a three-dimensional human skin model, comprising a reconstructed epidermis with a functional stratum corneum.

The test was performed as follows:

- Tissues were conditioned by pre-incubation for 43 hours 44 minutes.
- Tissues were transferred to fresh maintenance medium and topically exposed with the test chemical (19.8 mg + 19.8 μL of 0.9% NaCl), or negative and positive control (39.7μL) for 3 minutes and/or 1 hour.
- After exposure, tissues were rinsed and blotted. Assay medium was replaced by MTT-medium.

- After 3 hours incubation, tissues were washed with phosphate buffer saline solution and the blue formazan salt was extracted with isopropanol. The optical density of the formazan extract was determined spectrophotometrically at 550 nm ± 10 nm.

1.11 PRESENTATION AND ANALYSIS OF RESULTS

1.11.1 Presentation of results

Cell viability was calculated for each tissue as % of the mean of the negative control tissue. Skin corrosivity potential of test item is classified according to the remaining cell viability obtained after 3 minutes and / or 1 hour exposure.
The optical density (OD) values and calculated percentage cell viability data for the test item, the positive and the negative controls were reported in tabular form including mean values.

1.11.2 Analysis of results

The optical density (OD) values obtained for each test item were used to calculate percentage viability relative to the negative control, which is arbitrarily set at 100%. Test item was classified as corrosive or non-corrosive on the basis of the results obtained in accordance with OECD Guideline No. 431 (April 13, 2004) and subsequent amendments Table 1.2, page 16.

Table 1.2 Prediction of corrosivity

Classification	Criteria for In Vitro interpretation
Corrosive	If viability <50% after 3 min exposure or If viability ≥50% after 3 min exposure and <15% after 1 hour
Non-corrosive	If viability ≥50% after 3 min exposure and ≥15% after 1 hour

1.11.3 Data recording

Both qualitative and quantitative individual data were collected using RS/1 software (release 6.3, APPLIED MATERIALS).

1.12 QUALITY ASSURANCE

The Quality Assurance Unit confirmed that operating procedures governing studies are strictly applied, by periodic in-study audits. These audits are undertaken at random over the course of the year according to CERB internal SOPs. The experimental report in English and data were audited by Quality Assurance Unit, in accordance with the standard procedures of the Centre.

1.13 ARCHIVES

1.13.1 Archives of records

The study plan, raw data, correspondence and the report will be stored for 10 years at CERB - 18800 Baugy, France, starting from the date of the final report. Quality Assurance reports will be stored at the Testing Facility without time limit.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- continued storage of records
- return of records to the Sponsor
- destruction of records

1.13.2 Archives of test item

One sample of the test item (1 g approximately) at the end of the study will be stored for 10 years at CERB - 18800 Baugy - France, starting from the date of the final report.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- return of sample to the Sponsor
- destruction of sample

PART II
EXPERIMENTAL RESULTS

2.1 REPORT OF RESULTS

2.1.1 Preliminary study

Since MTT solution did not turn blue/purple when in contact with the test item for 1 hour (step 1), no interference between MTT and test item was concluded. For this reason, the second step of the preliminary study was not undertaken.

2.1.2 Main study

Mean and individual values are presented on page 21.

After 3 minutes of treatment, the positive control item showed a decrease in cell viability percentage of -84% when compared with the negative control, which is arbitrarily set at 100%.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was similar to that of the negative control group, in both cases (*i.e.* +6% and +24%, respectively).

2.2 DISCUSSION

As the positive control item after 3 minutes of treatment showed a decrease in cell viability percentage of -84% when compared with the the negative control, the calculated cell viability percentage was 16%.
As positive control group showed a cell viability value less than 50%, it was classified as corrosive as expected and according to the OECD Guideline No.431. This result validated the ongoing sensitivity of the method used.

After 3 minutes and 1 hour of treatment with the undiluted test item, the percentage of cell viability was close to 100% in both cases (*i.e.* +6% and +24% respectively). This scale of variation is minor and and can be attributed to inter-individual variation of reconstructed epidermis. Since the test item was not presumed to interfere with the MTT endpoint (*i.e.* preliminary study), the cell viability was set at 100% in both cases.

After 3 minutes and 1 hour of treatment with the undiluted test item, as cell viability values were more than 50% and more than 15% respectively, the test item was classified as non-corrosive.

Results are summarised in Table 2.1, page 20:

Table 2.1 Cell viability and prediction of corrosivity

Treatment	Viability (%) T=3 min	Viability (%) T=1 hour	Classification
Negative control (NaCl 0.9%)	100	100	Non-corrosive
Test item	100	100	Non-corrosive
Positive control (KOH 8 mol/L)	16	/	Corrosive

Test item: Sample 3 Farmed red mud 2015
Cell viability is calculated for each tissue as % of the mean of the negative control tissue.
Electronic authentication: approved by Armelle Bouchard on 04-JAN-2016 at 11:29:24.802
Study 20150162TCUC

2.3 CONCLUSION

Under the experimental conditions adopted, Sample 3 Farmed red mud 2015 (batch No. Q3) was classified as non-corrosive on the SkinEthic human reconstructed epidermis.

OPTICAL DENSITY: INDIVIDUAL AND MEAN VALUES

Table 2.2 Optical density - Positive control (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.409	1.183
	SEM	0.029	0.034
	N	15	9
Positive control	Mean	0.222	NA
	SEM	0.014	NA
	N	9	0
	%	-84	NA

No statistical analysis.
NA: not applicable
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 18:24:47.635
Study 20150162TCUC

Table 2.3 Optical density - Positive control (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
	E6	1.579	NE
	F6	1.223	NE
	E7	1.454	NE
	F7	1.464	NE
	E8	1.514	NE
	F8	1.516	NE
Positive control	E9	0.282	NE
	F9	0.276	NE
	G9	0.256	NE
	E10	0.183	NE
	F10	0.183	NE
	G10	0.172	NE
	E11	0.226	NE
	F11	0.212	NE
	G11	0.208	NE

NE: not evaluated
Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 18:24:47.635
Study 20150162TCUC

Table 2.4 Optical density (mean values)

Treatment		T=3min	T=1h
Negative control	Mean	1.376	1.183
	SEM	0.032	0.034
	N	9	9
Sample 3 Farmed red mud 2015	Mean	1.454	1.465
	SEM	0.027	0.025
	N	9	9
	%	+6	+24

No statistical analysis.
Electronic authentication: created by Karine Guedes on 10-DEC-2015 at 18:32:49.901
Study 20150162TCUC

Table 2.5 Optical density (individual values)

Treatment	Well number	T=3min	T=1h
Negative control	B2	1.352	1.274
	C2	1.369	1.299
	D2	1.434	1.323
	B3	1.175	1.036
	C3	1.303	1.120
	D3	1.363	1.102
	B4	1.439	1.162
	C4	1.447	1.102
	D4	1.505	1.232
Sample 3 Farmed red mud 2015	E2	1.360	1.352
	F2	1.397	1.405
	G2	1.414	1.451
	E3	1.384	1.420
	F3	1.423	1.502
	G3	1.445	1.596
	E4	1.567	1.435
	F4	1.517	1.479
	G4	1.580	1.541

Electronic authentication: validated for statistical analysis by Karine Guedes on 10-DEC-2015 at 18:32:49.901
Study 20150162TCUC

APPENDICES

Appendix A

CERTIFICATE OF ANALYSIS OF TEST ITEM

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CERB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

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Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

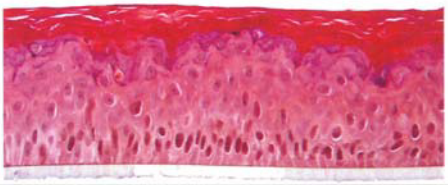
Appendix B

CERTIFICATE OF ANALYSIS OF RECONSTRUCTED EPIDERMIS

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS
RECONSTRUCTED HUMAN EPIDERMIS

CCE-093-RHE D17-S/01

Description:	**Reconstructed Human Epidermis (RHE/S/17)**		
	0.5 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on inert polycarbonate filters in chemically defined medium, for 17 days.		
Usage:	**FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN**		
Storage:	This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO_2 with saturated humidity.		
Passage:	Second (strain n° PK2 PKP.E-12)		
Batch N°:	**15-RHE-145**		
Origin:	Foreskin		
Histology:	 **Control n° E152173**		
Quality Controls:	**Test**	**Specification**	**Result**
	Histological observation (HES stained vertical paraffin sections, n=5)	Number of cell layers ≥ 4 Absence of significant histological abnormalities	**6 cell layers** Absence of significant histological abnormalities
		Well differentiated epidermis consisting of basal, spinous, granular layers and a stratum corneum	Satisfactory
	Cell viability (570 nm optical density, MTT test, n=2)	O.D. > 0.7	**O.D. = 1.1** (CV = 2.2 %)
	Barrier function integrity test (Exposure Time inducing 50% viability using Triton X-100 1%, n =12)	4.0h ≤ ET50 ≤ 10.0h	**5.4** h
Biological safety:	On blood of the same donor, we have verified: . the absence of HIV1 and 2 antibodies . the absence of hepatitis C antibodies . the absence of hepatitis B antigen HBs On epidermal cells of the same donor, we have verified: . the absence of mycoplasma		
Expiration date	December 7, 2015.		

"The use of this human tissue is strictly limited to in vitro testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited"

Lyon, December 1, 2015.
Certified and released by
Julie BIDOGGIA, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
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Farmed Bauxite Residue, Q2 2019

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL

(EPISKIN™/MTT method)

FINAL REPORT

ERBC STUDY NO. A4245

Sponsor:
Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

COMPLIANCE STATEMENT

I, the undersigned, was responsible for the preparation of this report and hereby declare that it constitutes a true and faithful account of the procedures adopted and of the results obtained in the performance of the study. The aspects of the study conducted by European Research Biology Center S.r.l. were performed in accordance with:

1. Decreto Legislativo 2/3/2007 n. 50, Attuazione delle direttive 2004/9/CE e 2004/10/CE, concernenti l'ispezione e la verifica della Buona Pratica di Laboratorio (BPL) ed il ravvicinamento delle disposizioni legislative, regolamentari ed amministrative relative all'applicazione dei principi di Buona Pratica di Laboratorio ed al controllo della loro applicazione per le prove sulle sostanze chimiche (G.U. 13/4/2007, Serie generale n. 86) and subsequent revisions.
2. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004, on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances.
3. ENV/MC/CHEM(98)17 OECD principles on Good Laboratory Practice (as revised in 1997).

DIGITAL SIGNATURE

L. Bisini, Biol.D.
STUDY DIRECTOR

Date

KEY STUDY STAFF

L. Bisini	Study Director
R. Zanier	Head of Quality Assurance
S. Cinelli	Associate Scientific Director, Head of Genetic Toxicology & Alternative Methods

Test Facility Management

S. Venturella, Biol.D., ERT	Test Facility Director

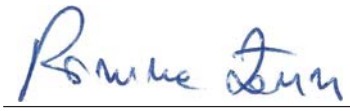
QUALITY ASSURANCE STATEMENT

Study phases	Inspection dates	Report to SD[a]	Report to CM[b]
Study Plan			
Study Plan check	11.02.2021	15.02.2021	15.02.2021
Study Plan Amendment check	18.03.2021	18.03.2021	18.03.2021
Process based inspections related to this type of study			
Dose preparation	18.01.2021	-	03.03.2021
Treatment	18.03.2021	-	19.03.2021
Final Report (end of review)	*date of QA Statement signature*		

[a] *SD = Study Director only for protocol check and study based inspections*
[b] *CM = Company Management*

Other QA process based inspections were carried out on departments or laboratories performing routine activities (e.g. Analytical Chemistry, Histopathology, Veterinary Services and Clinical Pathology) as well as on other routine activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here. Involved departments or laboratories and support functions are also subject to regular facility inspections.

Review of this report by ERBC QA found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.



7th September 2021

R. Zanier, CMB, Ph.D.
HEAD OF QA

Date

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1 SUMMARY

The potential of the test item Farmed Bauxite Residue, Q2 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™. The experimental procedures are based on the OECD Guideline for testing of chemicals no. 431. The test item, as well as controls, were tested for their ability to impair cell viability after an exposure period of 3, 60 and 240 minutes. The final endpoint of the assay is the colorimetric measurement of MTT reduction (blue formazan salt) in the test system, being this reaction an index of cell viability. The test item was tested as supplied by the Sponsor.

A preliminary test was carried out to evaluate the compatibility of the test item with the test system. In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Therefore, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

In the Main Assay, for each treatment time, the test item (physical state: solid) was applied as supplied in two replicates, at the treatment level of 20±2 mg/*epidermis* unit, each measuring 0.38 cm^2 (treatment level: 52.6 mg/cm^2). Positive and negative controls (Glacial acetic acid and Physiological saline, respectively) were concurrently tested, in the same number of replicates and test conditions at the treatment level of 50 µL/*epidermis* unit. Positive control was included only at the longest treatment time of 240 minutes, while a negative control was included for each treatment time.

In the Main Assay, the negative controls gave the expected baseline value (Optical Density values ≥ 0.6 and ≤ 1.5) and variability (difference of viability between the two replicates lower than 30%), at each treatment time, in agreement with the guideline indications. For each treatment time, the concurrent negative control mean value is considered the baseline value of the treatment series and thus represents 100% of cell viability.

The positive control caused the expected cell death (0% of cell viability, when compared to the negative control).

Based on the stated criteria, the assay was regarded as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 60 and 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the concurrent blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	92
60	61
240	50

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q2 2019 is identified as non-corrosive to the skin.

2 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the potential skin corrosion of the test item as measured by its ability to induce cell death in a commercial reconstructed human epidermis (RhE) model, EPISKIN™.

2.2 Regulatory compliance

Experimental procedures were based on the following guideline:

- OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method" (Adopted on 18 June 2019).

The Sponsor affirmed that the test item is a chemical product (industrial waste) and that the study was performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

2.3 Principle of the test

The test system EPISKIN™ is a reconstructed human epidermis (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.*, the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue; CAS N. 298-93-1] into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2.4 Sponsor and Test Facility

The study was performed at:

European Research Biology Center S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

On behalf of the Sponsor:

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

2.5 Study schedule

Procedure	**Date**
Protocol approved by: Study Director	09 February 2021
Start of experimental phase Preliminary test	11 February 2021
End of experimental phase Completion of scoring of Main Assay	19 March 2021
Study completion	Date of Study Director's signature on this report

3 TEST ITEM AND CONTROL ITEMS

3.1 Test Item

3.1.1 Identity

Details of the test item received at ERBC were as follows:

Identity	Farmed Bauxite Residue, Q2 2019
Label name	Farmed Bauxite Residue
Batch no.	Q2 2019
Expiry date	January 2022
Storage conditions	Room temperature
ERBC no.	17295

The determination of the identity, strength, purity, composition and stability of the test item and the quality system under which the test item characterisation was performed was the responsibility of the Sponsor. The certificate of analysis is presented in Addendum 1 of this report. A sample of test item was taken and will be stored in the archives of ERBC for 10 years prior to disposal.

3.2 Control Items

Positive control item was Glacial acetic acid (C. Erba, batch no. P8B028018C).

Negative control item was Physiological saline (Baxter, batch no. 19H0603).

Positive and negative control items were obtained commercially and characterised by labelling. Determination of the stability and concentration of solutions of positive and negative controls were not undertaken, since it is sufficient to provide evidence for the correct expected response of the test system to them.

4 METHODS

4.1 Test System

4.1.1 EPISKIN™

Commercial Name	EPISKIN™ - 0.38 cm^2
Supplier	SkinEthic Laboratories (4, A. Fleming – 69366 Lyon – France)
Batch	21-EKIN-011
Arrived at ERBC on	16 March 2021

Functional controls

Quality controls: histology scoring, magnitude of viability and barrier function (IC_{50} determination).

Biological safety: absence of HIV1 and 2 antibodies, hepatitis C antibodies, hepatitis B antigen HBs, absence of bacteria, fungi and mycoplasma.

A certificate of analysis can be found in Addendum 2.

4.1.2 Preparation of the Test System

Examination before use

Temperature indicator: pale grey (suitable for use)

pH indicator: orange (suitable for use)

Preparation and pre-treatment incubation period

At arrival all kit components were maintained at +4 °C, until use. According to the supplier procedure, within 24 hours from arrival, plates were opened under a sterile airflow and each insert, containing the epidermal tissue, was carefully taken out and placed in a 12-well plate in which each well had previously been filled with 2 mL/well SkinEthic Maintenance Medium. Culture plates were placed in the incubator at 37°C, 5% CO_2 and saturated humidity for approximately 24 hours.

4.2 Media

Maintenance Medium	SkinEthic; batch: 21-MAIN3-011
Assay Medium	SkinEthic; batches: 21 ESSC 006 and 21 ESSC 011

4.3 Experimental procedure

4.3.1 Preliminary test

Direct MTT reduction test (Step 1)

Non-specific reduction of MTT was evaluated as follows: two mL of MTT ready-to-use solution (0.3 mg/mL) was incubated with 20±2 mg of test item at 37 °C, 5% CO_2 and saturated humidity for 3 hours, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time was carried out.

Colouring potential test (Step 2)

Chemicals' colouring potential was assessed for potential interaction with the test system. 10±1 mg of test item was added to 90 µL of distilled water (Eurospital; batch no. 20C3004) in a transparent tube and the resulting solution/suspension mixed by using a vortex for 15 minutes. Colouring of the solution/suspension at the end of the incubation time was evaluated by unaided eye.

4.3.2 Main Assay

Treatment

In Main Assay, alive tissues were treated with the test item, positive and negative controls. The treatment scheme was the following:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Negative control	Live tissue	Physiological saline	3	50 µL	2	CN1A, CN1B
Negative control	Live tissue	Physiological saline	60	50 µL	2	CN2A, CN2B
Negative control	Live tissue	Physiological saline	240	50 µL	2	CN3A, CN3B
Positive control	Live tissue	Glacial acetic acid	240	50 µL	2	CP1A, CP1B
Test item	Live tissue	Farmed Bauxite Residue, Q2 2019	3	20±2 mg	2	TI-A1A, TI-A1B
Test item	Live tissue	Farmed Bauxite Residue, Q2 2019	60	20±2 mg	2	TI-A2A, TI-A2B
Test item	Live tissue	Farmed Bauxite Residue, Q2 2019	240	20±2 mg	2	TI-A3A, TI-A3B

Additional controls were included in the Main Assay with the following treatment scheme:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Test itemwithout MTT	Live tissue	Farmed BauxiteResidue, Q2 2019	3	20±2 mg	2	CC-A1A, CC-A1B
Test itemwithout MTT	Live tissue	Farmed BauxiteResidue, Q2 2019	60	20±2 mg	2	CC-A2A, CC-A2B
Test itemwithout MTT	Live tissue	Farmed BauxiteResidue, Q2 2019	240	20±2 mg	2	CC-A3A, CC-A3B

Results presented in this report are obtained in a repeated assay. In the original one, not acceptable negative control values were obtained. Data from the original experiment are not presented in this report but are ratained in the study file and will be archived as indicated in the study protocol.

Exposure period

Exposure times of 3, 60±5 and 240±5 minutes were allowed in a ventilated cabinet at room temperature.

Washing

At the end of the exposure, each tissue was rinsed with approximately 25 mL of sterile PBS, filling and empting the tissue insert. The excess liquid was carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of maintenance medium.

MTT staining

Each tissue insert was incubated with 2 mL/well of MTT ready-to-use solution. Plates were incubated for 3 hours ± 5 minutes at 37°C, 5% CO_2 and saturated humidity. At the end of the incubation period, tissues were placed on absorbent paper to dry. A total biopsy was carried out by means of a biopsy punch to allow biopsies of the same dimensions.

The epidermis were separated from the collagen matrix and both placed in a microtube prefilled with 500 µL of acidic isopropanol. Tubes were mixed by vortexing and preserved overnight at room temperature to allow formazan extraction. At the end of the extraction period, debris were eliminated by short centrifugation of the tubes (14000 rpm for 2 minutes) and aliquots of 200 µL from each sample were read in duplicate for their absorbance at 595 nm. Six aliquots (200 µL) of acidic isopropanol were analysed and used as blank. An MTT formazan calibration curve was performed in order to ensure that OD values obtained in the main experiment were within the spectrophotometer linear range.

4.4 Analysis and evaluation of data

4.4.1 Study Acceptability Criteria

The assay was considered valid if the following criteria were met:

- Blank controls: mean OD value < 0.1.
- Negative controls: mean OD value ≥ 0.6 and ≤ 1.5.
- Positive controls: mean viability expressed as percentage of the negative control ≤ 20%.
- In the range of 20-100% viability and for ODs ≥ 0.3, difference of viability between the two, tissue replicates should not exceed 30%.

4.4.2 Interpretation of results and classification

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, mean relative viability values (percentage relative to the concurrent negative control) were calculated.
Cut-off values for the endpoint of the test are established as follows:

Criteria	Classification
< 35% after 3 min exposure	Corrosive Sub-categoria 1A
≥ 35% after 3 min exposure AND < 35% after 60 min exposure OR ≥ 35% after 60 min exposure AND < 35% after 240 min exposure	Corrosive: combination of sub-categories 1B and 1C
≥ 35% after 240 min exposure	Non- Corrosive

For colouring test items, Non Specific Colour (NSC_{living}) relative to the D-PBS Control is evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{test\ item(not\ incubated\ with\ MTT)}}{OD_{negative\ control\ living\ tissues}}$$

If the $NSC_{living} \leq 5\%$ only blank subtraction is carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction is carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

4.5 Protocol deviations

No deviation occurred during the study.

4.6 Archives

Full records of all aspects of the study conduct were maintained together with the results of all measurements and observations. All specimens, raw data, records and documentation generated during the course of this study will be retained within ERBC archives. The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. The Final Protocol, the Final Report and, where applicable, electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower), will be archived at ERBC.

5 RESULTS

5.1 Preliminary test

Before the Main Assay, a preliminary test was carried out to evaluate the compatibility of the test item with the test system. Results of this preliminary test can be found in Table 1.

In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. Thus no additional controls were added in the main phase for the evaluation of MTT non-specific reduction. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Thus, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

5.2 Main Assay

A Main Assay was performed. Raw data and data elaboration are reported in Table 2.

The mean Optical Density of Blank Controls was 0.036, lower than the maximum acceptable value (0.1). All negative control mean OD values gave the expected baseline value and variability, in agreement with guideline indications. According to the method, each negative control mean value is considered the baseline value for the concurrent treatment series, thus they represent 100% of cell viability.

Positive control results indicated an appropriate cell death with an acceptable relative cell viability (0% of the negative control value).

Based on the stated criteria, the study was accepted as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 60 and 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	92
60	61
240	50

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q2 2019 is identified as non-corrosive to the skin.

6 CONCLUSION

The potential of the test item Farmed Bauxite Residue, Q2 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.

The blank, negative and positive controls gave acceptable results at all treatment times, thus the study was accepted as valid.

The mean cell viability of the test item treated tissues, after the blank subtraction, was higher than 35% at all treatment times. Based on these results, the test item Farmed Bauxite Residue, Q2 2019 is identified as non-corrosive to the skin.

7 TABLES

Farmed Bauxite Residue, Q2 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN^{TM}/MTT method)

STUDY NO.: A4245

PRELIMINARY TEST

Direct MTT reduction test (Step 1)

Test item (mg)	**MTT ready to use solution (mL)**	**Container**	**Incubation condition**	**Colour Observation**
20 ± 2	2.0	well	3 h at 37°C, 100% nominal humidity 5% CO_2	Red/brown suspension, with brow precipitate (no interaction)

Colouring potential test (Step 2)

Test item (mg)	**Water (µL)**	**Container**	**Incubation condition**	**Colour Observation**
10 ± 1	90	Eppendorf tube	15', ambient condition, in agitation	Brown suspension (possible interaction)

Farmed Bauxite Residue, Q2 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4245

MAIN ASSAY

TREATMENT TIME: 3 minutes

BLANK		**Negative Control**					
	OD_{blank}				**OD_{NC}**		**Viability (%)**
	0.0368	CN1A-1	0.6893	0.6530	0.6874		97.5
	0.0364	CN1A-2	0.7582	0.7219			
	0.0364	CN1B-1	0.7556	0.7193	0.7230		102.5
	0.0363	CN1B-2	0.7631	0.7268			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.705	**Mean** 0.705		100
SD	0.0003	**SD**		0.035			
CV(%)	0.84	**CV(%)**		5.0		**Δ (%)**	5.0

Test Item					
				OD_{TI}	**Viability (%)**
TI-A1A-1	0.8159	0.7796	0.7067		100.2
TI-A1A-2	0.6702	0.6339			
TI-A1B-1	0.6534	0.6171	0.5973		84.7
TI-A1B-2	0.6138	0.5775			
Mean		0.652	**Mean** 0.652		**92**
SD		0.088			
CV(%)		13.5		**Δ (%)**	16.8

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-A1A-1	0.0482	0.0119	0.0081		1.2
CC-A1A-2	0.0407	0.0044			
CC-A1B-1	0.0406	0.0043			
CC-A1B-2	0.0409	0.0046	0.0044		0.6
Mean		0.006	**Mean** 0.006		**1**
SD		0.004			
CV(%)		59.4		**Δ (%)**	58.9

Farmed Bauxite Residue, Q2 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4245

MAIN ASSAY

TREATMENT TIME: 60 minutes

BLANK

	OD_{blank}
	0.0368
	0.0364
	0.0364
	0.0363
	0.0361
	0.0359
Mean	0.036
SD	0.0003
CV(%)	0.84

Negative Control

				OD_{NC}		Viability (%)
CN2A-1	0.8525	0.8162		0.8404		97.7
CN2A-2	0.9009	0.8646				
CN2B-1	0.9044	0.8681		0.8796		102.3
CN2B-2	0.9275	0.8912				
Mean		0.860	**Mean**	0.860		100
SD		0.032				
CV(%)		3.7			**Δ (%)**	4.6

Test Item

			OD_{TI}		Viability (%)
TI-A2A-1	0.5555	0.5192	0.5309		61.7
TI-A2A-2	0.5790	0.5427			
TI-A2B-1	0.5625	0.5262	0.5268		61.3
TI-A2B-2	0.5638	0.5275			
Mean		0.529	**Mean** 0.529		**61**
SD		0.010			
CV(%)		1.9		**Δ (%)**	0.8

Test Item without MTT

			ODcc		NSCliving (%)
CC-A2A-1	0.0431	0.0068	0.0197		2.3
CC-A2A-2	0.0690	0.0327			
CC-A2B-1	0.0702	0.0339	0.0339		3.9
CC-A2B-2	0.0703	0.0340			
Mean		0.027	**Mean** 0.027		**3**
SD		0.013			
CV(%)		49.9		**Δ (%)**	52.9

Farmed Bauxite Residue, Q2 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4245

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**						
	OD_{blank}					**OD_{NC}**		**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582		111.2
	0.0364	CN3A-2	1.0535	1.0172				
	0.0364	CN3B-1	0.9424	0.9061		0.8453		88.8
	0.0363	CN3B-2	0.8208	0.7845				
	0.0361							
	0.0359							
Mean	0.036	**Mean**		0.952	**Mean**	0.952		100
SD	0.0003	**SD**		0.137				
CV(%)	0.84	**CV(%)**		14.4			**Δ (%)**	22.4

Test Item						
				OD_{TI}		**Viability (%)**
TI-A3A-1	0.4708	0.4345		0.4834		50.8
TI-A3A-2	0.5686	0.5323				
TI-A3B-1	0.4931	0.4568		0.4673		49.1
TI-A3B-2	0.5142	0.4779				
Mean		0.475	**Mean**	0.475		**50**
SD		0.042				
CV(%)		8.8			**Δ (%)**	3.4

Test Item without MTT						
				ODcc		**NSCliving (%)**
CC-A3A-1	0.0408	0.0045		0.0061		0.6
CC-A3A-2	0.0440	0.0077				
CC-A3B-1	0.0411	0.0048		0.0041		0.4
CC-A3B-2	0.0398	0.0035				
Mean		0.005	**Mean**	0.005		**1**
SD		0.002				
CV(%)		35.3			**Δ (%)**	38.2

Farmed Bauxite Residue, Q2 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4245

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582	111.2
	0.0364	CN3A-2	1.0535	1.0172			
	0.0364	CN3B-1	0.9424	0.9061		0.8453	88.8
	0.0363	CN3B-2	0.8208	0.7845			
	0.0361						
	0.0359						
Mean	0.0363	**Mean**		0.952	**Mean**	0.952	100.0
SD	0.0003	**SD**		0.137			
CV(%)	0.84	**CV(%)**		14.4		**Δ (%)**	22.4

	Positive control				
				OD_{TI}	**Viability (%)**
	CP1A-1	0.0386	0.0023	0.0019	0.2
	CP1A-2	0.0379	0.0016		
	CP1B-1	0.0382	0.0019	0.0021	0.2
	CP1B-2	0.0386	0.0023		
Mean			0.002	**Mean** 0.002	**0**
SD			0.0003		
CV(%)			16.9	**Δ (%)**	7.47

8 ADDENDA

RUSAL
AUGHINISH

Aughinish Alumina Ltd.
Aughinish Island
Askeaton
Co. Limerick
IRELAND

CERTIFICATE OF ANALYSIS

Sample Type : Farmed bauxite residue
Sample mass : 10g (approx.) per sample
Report Issued : 12/03/2021

Sample	% Moisture	Units	Method
Farmed Bauxite Residue, Q2 2019	27.5	%w/w	ATM047
Farmed Bauxite Residue, Q4 2019	23.0	%w/w	ATM047
Farmed Bauxite Residue, Q1 2020	24.0	%w/w	ATM047
Farmed Bauxite Residue, Q4 2020	21.4	%w/w	ATM047

Jason Clohessy

LABORATORY QUALITY MANAGER
Jason Clohessy

"This report relates only to the items tested and shall not be reproduced except in full and with the approval of the Laboratory of Aughinish Alumina Ltd".

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS

CCE-091-SM D13-S/04

NAME

EpiSkin™ Small / Human Epidermis (SM/13)

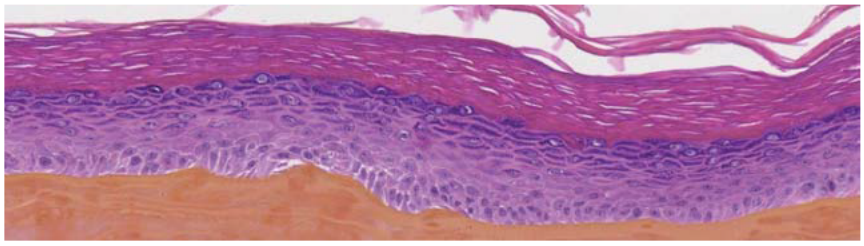
DESCRIPTION

0.38 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on a collagen matrix, for 13 days

BATCH : **21-EKIN-011**
ORIGIN : Adult donors
USAGE : FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN
STORAGE : This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO2 with saturated humidity

QUALITY CONTROLS

Control # E210333

	Process	Specification	Result
HISTOLOGY	HES stained paraffin section	Multi-layered, highly differentiated epidermis consisting of organized basal, spinous and granular layers, and a multilayered *stratum corneum*	**Satisfactory**
		Number of cell layers ≥ 4	**7.5 cell layers**
			
IC50 DETERMINATION	SDS concentration, MTT test.	1.5 mg/mL ≤ IC50 ≤ 3.0 mg/mL	**1.9 mg/mL**

BIOLOGICAL SAFETY:

On blood of the donors, we have verified the absence of HIV1 and 2 antibodies, hepatitis C antibodies and hepatitis B antigen HBs.
On cells from the donors, we have verified the absence of bacteria, fungus and mycoplasma.

SUGGESTED EXPIRATION DATE:

March 22, 2021

Lyon, March 16, 2021
Certified and released by Michel BATAILLON, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

The use of this human tissue is strictly limited to *in vitro* testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

THE
NON-CLINICAL
ENGINE
EUROPEAN RESEARCH BIOLOGY CENTER

Version 20/2

Farmed Bauxite Residue, Q2 2019
***IN VITRO* SKIN CORROSION STUDY USING A**
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

Protocol Amendment 1
prepared for

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

by

EUROPEAN RESEARCH BIOLOGY CENTER S.r.l.
Via Tito Speri, 12/14
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Società a socio unico soggetta a direzione e coordinamento di ERBC SA, Chemin de Montifault, 18800 Baugy (Francia)
www.erbc-group.com

This Protocol Amendment contains changes to the following portions of the original Final Protocol signed on 09 February 2021.
If necessary/applicable, numbering of sections and/or pages may change according to the insertions or deletions applied.
Any changes related to the current amendment are indicated directly in the relevant section/s of the document as follows: any additions are indicated in **bold and underlined** text and any deletions in ~~double strikethrough~~ text. The history of previous changes is indicated below:

Amendment and Section(s)	**Date of issue and Reason for Change**
Amendment 1	**Date of Study Director Signature:** 17 March 2021
Page 6, § 4.1.3 Preparation and storage of the test system	Change of procedure due to organizational problems

IN VITRO SKIN CORROSION STUDY USING A
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

MANAGEMENT OF STUDY

Study Director	:	L. Bisini, Biol.D. lbisini@erbc-group.com
Sponsor	:	Aughinish Alumina Ltd. Aughinish island, Askeaton Co. Limerick Ireland
Monitor	:	R. O'Dwyer

QUALITY ASSURANCE

Head of QA & GXP Compliance	:	R. Zanier, CMB, Ph.D.

LOCATION OF STUDY

The study will be performed at	:	European Research Biology Center S.r.l. Via Tito Speri, 12/14 00071 Pomezia Italy

The laboratory facilities, archives and administration are located at this site.

PROJECTED TIME PLAN

			Date
1.	Proposed experimental starting date	:	First half of February 2021
2.	Proposed experimental completion date	:	2 weeks from the start of the experimental phase
3.	QA-Audited Draft Report to Sponsor	:	2 weeks after the end of the experimental phase

Any change in the experimental design or any additional activity requested to maintain the scientific or regulatory integrity of the study might cause a change in time schedule indicated above.

1. INTRODUCTION

1.1 Objective

This test allows the identification of non-corrosive and corrosive substances and mixtures in accordance with the UN GHS (1). The test system EPISKIN™ is one of the available commercial reconstructed human *epidermis* (RhE) models used for distinguishing corrosive (C) from non-corrosive (NC) substances. It further supports the sub-categorization of corrosive substances and mixtures into optional Sub-category 1A, in accordance with the UN GHS, as well as a combination of Sub-categories 1B and 1C.

1.2 Regulatory requirements

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 50 of 2 March 2007 and subsequent revisions.

The Sponsor has affirmed that the test item is a chemical product (industrial waste) and that the study will be performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

In addition, the study is designed to comply with the experimental methods indicated in the guidelines of:

OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (Rhe) Test Method" (Adopted on 18 June 2019);

1.3 Principles of the method

The test system EPISKIN™ is a reconstructed human *epidermis* (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.,* the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue], into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item and the quality system under which the test item characterisation was performed will also be the Sponsor's responsibility.
A certificate of analysis for the test item should be supplied.

2.2 Identity

The test item will be Farmed Bauxite Residue, Q2 2019.

The following information, supplied by the Sponsor, refers to the original batch of test item received for the study:

Batch number: Q2 2019
Expiry date: not available
Storage conditions: room temperature

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used will be recorded according to standard procedures.

2.3 Preparation of test item

Test item will be used in the form supplied.
If necessary, solid substances will be ground to reduce particle size and aid suspension.

2.4 Safety precautions

The precautions necessary when handling the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under ERBC Hazard Classification System, according to ERBC standard procedures.

2.5 Disposal

Approximately 1 year after the Final Report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration or returned to the Sponsor.

3. CONTROL ITEMS

3.1 The control items are commercially obtained by ERBC. Information about the identity, strength, purity and composition or other characteristics appropriately defining these compounds, before their use in the study, as well as the stability are detailed in documents obtained from the Supplier.

3.2 Control items will be the following:
- Negative control: The preferred choice will be 0.9% (w/v) NaCl, but Distilled Water (Bieffe Medital or equivalent) can be used, if necessary.
- Positive control item: Glacial Acetic Acid.

Determination of the stability and concentration of solutions of these agents will not be undertaken since it is sufficient to provide evidence of the correct expected response of the test system to them.

4. MATERIALS AND METHODS

4.1 EPISKIN™

The test system EPISKIN™ is commercially available from SkinEthic Laboratories.

4.1.1 Characteristic of the test system

The SkinEthic reconstructed human tissue model EPISKIN™ consists of an airlifted, living, multi-layered tissue construct, produced in polycarbonate inserts in serum-free and chemically defined medium, featuring normal ultra-structure and functionality equivalent to human tissue *in vivo*.
Normal human keratinocytes are used to reconstruct the epithelium. Multiple layers of viable epithelial cells (basal layer, *stratum spinosum, stratum granulosum*) should be present under a functional *stratum corneum*. *Stratum corneum* should be multilayered containing the essential lipid profile to produce a functional barrier with robustness to resist rapid penetration of cytotoxic marker chemicals.

4.1.2 Functional conditions

The barrier function should be demonstrated. The containment properties of the RhE model should prevent the passage of material around the *stratum corneum* to the viable tissue, which would lead to poor modelling of skin exposure.
The RhE model supplier should ensure that each batch of the RhE model used meets defined production release criteria. A certificate will be supplied for each batch of the test system.

4.1.3 Preparation and storage of the test system

Within 24 hours from arrival ~~Immediately after arrival~~, the multiwell plate will be opened under a sterile airflow. Each insert containing the epidermal tissue will be carefully taken out. Any remaining agarose that adheres to the outer sides of the insert will be rapidly removed by gentle blotting on the sterile filter paper. Inserts will be quickly placed in a 12-well plate in which each well has previously been filled with 2 mL/well SkinEthic Maintenance Medium (pre-warmed at 37 °C) making sure that no air bubbles are formed underneath the inserts.
Culture plates will be placed in the incubator at 37°C, 5% CO_2 and saturated humidity.
Testing can initiate after at least two hours of incubation.

4.2 Media and reagents

SkinEthic Maintenance Medium Supplied with the EPISKIN™
To be stored at 2-8°C. To be used at room temperature (without pre-heating).

SkinEthic Assay Medium To be stored at 2-8°C.	Supplied with the EPISKIN™
0.9% (w/v) NaCl	
Glacial Acetic Acid	
MTT Stock Solution	3 mg/mL MTT in D-PBS.
MTT Ready-to-use Solution	MTT Stock Solution diluted 1:10 (v/v) with pre-warmed SkinEthic Assay Medium (final concentration 0.3 mg/mL of MTT).
Acidic Isopropanol	0.04 N HCl in Isopropanol
Water-killed epidermis	to be prepared only for MTT interacting reagents. Living epidermis is incubated with 2 mL of distilled water at 37°C, 5% CO_2 and saturated humidity for approximately 2 days. The water is discarded and the samples frozen at -18 to -20°C for up to 6 months.

5. EXPERIMENTAL PROCEDURE

5.1 Experimental design

Before testing the test item for corrosive properties, adequacy of the test system will be verified to ensure that the test item enters in the applicability domain of the assay.
A preliminary test will be undertaken in two steps. The test item will be checked for the ability to reduce the MTT (Step 1) and to colour water (Step 2).
The main experiment will be carried out including all controls to assess corrosive potential and classify the test item, according to the EU/GHS regulations.

5.2 Preliminary test

5.2.1 Direct MTT reduction test (Step 1)

Non-specific reduction of MTT will be evaluated as follows:
Two mL of MTT Ready-to-use Solution will be incubated with an amount of the test item (50 µL if liquid, 20 ± 2 mg if solid) and incubated at 37°C, 5% CO_2 and saturated humidity for 3 hours protected from light, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time will imply the use of water killed epidermis as a control in the main assay (additional cost).

5.2.2 Colouring potential test (Step 2)

To identify potential interference by coloured test chemicals or test chemicals that become coloured when in contact with water and decide on the need for additional controls, spectral analysis of the test chemical in water should be performed.
An amount of the test item (10 µL if liquid, 10 ± 1 mg if solid) will be added to 90 µL of distilled water in a transparent tube (vial or micro-tube). The mixture will be blended for approximately 15 minutes and spectral analysis, if necessary, will be performed at 595 nm.
Colouring of the solution (e.g. observation of blue or purple appearance) at the end of the incubation time will imply the use of alive samples treated without MTT as a control in the main assay.

5.2.3 Further preliminary test (Additional cost)

When a positive result is obtained in preliminary tests described either in section 5.2.1 or 5.2.2 (or both), further preliminary test may be conducted to quantify the ability of the test item to reduce MTT or to stain tissue before beginning the main test. The results may indicate that the test item is not suitable for the test system before beginning a complete main assay. These assays will be conducted only in agreement with the Sponsor.
Otherwise, the Main Assay will be conducted with all the appropriate controls.

5.3 Main Assay

5.3.1 Treatment scheme

A Main Assay will be carried out including the test item, positive and negative controls. A typical treatment scheme may be the following:

Basic assay:

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Negative control 1	Live tissue	0.9% NaCl or distilled water	3	2
Negative control 2	Live tissue		60 (± 5)	2
Negative control 3	Live tissue		240 (± 5)	2
Positive control	Live tissue	Glacial acetic acid	240 (± 5)	2
Test item 1	Live tissue	Farmed Bauxite Residue, Q2 2019	3	2
Test item 2	Live tissue		60 (± 5)	2
Test item 3	Live tissue		240 (± 5)	2

Additional controls

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Test item 1 *	Killed tissue	Farmed Bauxite Residue, Q2 2019	3	2
Test item 2 *			60 (± 5)	2
Test item 3 *			240 (± 5)	2
Negative control 1 *	Killed tissue	0.9% NaCl or distilled water	3	2
Negative control 2 *			60 (± 5)	2
Negative control 3 *			240 (± 5)	2
Test item without MTT 1 §	Killed tissue	Farmed Bauxite Residue, Q2 2019	3	2
Test item without MTT 2 §			60 (± 5)	2
Test item without MTT 3 §			240 (± 5)	2
Test item without MTT 1 °	Live tissue	Farmed Bauxite Residue, Q2 2019	3	2
Test item without MTT 2 °			60 (± 5)	2
Test item without MTT 3°			240 (± 5)	2

* to be added in case of test items able to reduce MTT (killed tissue will be of the same batch but the batch will be different from the alive tissue batch).
° to be added in case of test items able to stain tissue or with a potential to stain tissue.
§ to be added in case of test items able both to stain tissue and reduce MTT.

Additional experiments could be performed if necessary.

5.3.2 Treatment procedure

A sufficient amount of the test or control item (50 ± 3 µL if liquid, 20 ± 2 mg if solid, 50 ± 2 mg if waxy/sticky) will be applied to uniformely cover each epidermis surface while avoiding an infinite dose. This will allow a surface exposure of approximately 131.6 µL or mg/cm^2 (liquid or waxy/stixy substances) or 52.6 mg/cm^2 (solid substances) being the treatment area of the commercial test system equal to 0.38 cm^2. Only for solid chemicals, the epidermis surface will be moistened with 100 ± 5 µL of 0.9% NaCl solution after application of the test item. Waxy/sticky test items will be added on each single tissue with a nylon mesh, if necessary.
The exposure time will be allowed in a ventilated cabinet at room temperature. For peculiar test items (e.g. surfactant and viscous liquids), an intermediate re-spreading will be carried out, if necessary.
Each tissue will then be rinsed with approximately 25 mL of sterile PBS filling and empting the tissue insert. The excess liquid will be carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of pre-warmed maintenance medium.

5.3.3 MTT Assay

The tissue inserts and controls will be incubated with 2 mL/well of MTT ready to use solution with the exception of treated tissues without MTT which will be incubated with SkinEthic Maintenance Medium.

Plates will be incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity.
At the end of the incubation period, tissues will be placed on absorbent paper to dry. A total biopsy will be carried out by means of a specific biopsy punch supplied by SkinEthic to allow biopsies of the same dimensions. The epidermis will be separated from the collagen matrix and will both be placed in a microtube prefilled with 500 µl of acidic isopropanol. In the case of coloured collagen, unstained and untreated collagen matrices taken from killed epidermis may substitute the coloured collagen.
Tubes will be mixed by vortexing and preserved overnight at room temperature to allow formazan extraction.
At the end of the extraction period, debris will be eliminated by short centrifugation of the tubes (e.g. at 10000-14000 rpm for 2 minutes).
Aliquots of 200 µl from each sample will be read in duplicate for their absorbance at 595 nm. Optical Density (OD) values will be recorded.
On the day of the analysis, the spectrophotometer will be verified against standard solutions of MTT formazan prepared in acidic isopropanol, in order to verify if the OD values fall in the linearity range of the spectrophotometer.

5.3.4 Special procedures for control wells

Control for potentially tissue-staining test items (killed/alive epidermis)
SkinEthic Assay Medium will be added to the test item-treated well instead of MTT solution. All other procedures will be carried out as described for the main assay.

Water killed epidermis control
Before use, tissues will be thawed by incubation at room temperature with 2 mL of SkinEthic Maintenance Medium for at least one hour. All other procedures will be carried out as described for the Main Assay.

6. EVALUATION OF RESULTS

6.1 Study acceptability criteria

Blank controls: mean OD value < 0.1
Negative controls (for each exposure time point): mean OD value ≥ 0.6 and ≤ 1.5
Positive controls: mean viability expressed as percentage of the negative control ≤ 20%
Intra-replicate variability: in the range 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

6.2 Interpretation of results and classification as corrosive

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, relative and mean relative viability values (percentage relative to the negative control) will be calculated.

Cut-off values for the endpoint of the test are established as follows:

Viability related to concurrent negative control	Classification
< 35% after 3 min exposure	**Corrosive:** • Sub-categoria 1A (optional)
≥ 35% after 3 min exposure **AND** < 35% after 60 min exposure **OR** ≥ 35% after 60 min exposure **AND** < 35% after 240 min exposure	**Corrosive:** • A combination of sub-categories 1B and 1C (optional)
≥ 35% after 240 min exposure	**Non-corrosive**

For direct MTT interacting test items, non specific MTT reduction calculation (NSMTT) relative to the Negative Control will be evaluated as follows:

$$NSMTT = 100 \times \frac{OD_{\text{treated killed tissues}} - OD_{\text{non-treated killed tissues}}}{OD_{\text{negative control living tissues}}}$$

The NSMTT control per exposure time will be performed concurrently to the testing of the coloured test item.
If the NSMTT ≤ 5% only blank subtraction will be carried out.
If 5% < NSMTT ≤ 50% blank and appropriate background subtraction will be carried out.
If NSMTT > 50% results should be taken with caution.

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control will be evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{\text{test item (not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

The NSC_{living} control per exposure time will be performed concurrently to the testing of the coloured test item and in case of multiple testing, an independent NSC control will be conducted with each test performed (in each run).
If the $NSC_{living} \leq 5\%$ only blank subtraction will be carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction will be carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

For test items able both to stain tissue and reduce MTT, to avoid a possible double correction for colour interference, a third control for Non Specific Colour in killed tissues (NSC_{killed}) will be evaluated per exposure time:

$$NSC_{killed} = 100 \times \frac{OD_{\text{test item (treated killed tissues not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

If the $[(NSMTT + NSC_{living}) - NSC_{killed}] \leq 5\%$ this value will not be considered for the final calculation.
If $5\% < [(NSMTT + NSC_{living}) - NSC_{killed}] \leq 50\%$ blank subtraction and appropriate background subtraction will be carried out.

If [(NSMTT + NSC_{living}) - NSC_{killed}] > 50% results should be taken with caution.

A single NSC_{killed} control is sufficient per test item regardless of the number of independent tests/runs performed, but should be performed concurrently to the NSMTT control.

The above corrections should be applied when the mean OD value of test item treated tissues without any correction is within the linearity range of the spectrophotometer. In case of strong interference (OD values out of the linear range) the test item is not suitable for this test method.

7. REPORTING

7.1 Presentation of data

The results will be presented in the form of tables.

7.2 Interim Report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.3 Final Report

A Draft Report will be sent to the Sponsor together with the Draft Report Approval Form. With the exception of signatures, the Draft Report will contain all information and data included in the Final Report.
Comments made by the Sponsor may be incorporated and the Final Report will be issued. If comments are not received within 6 months from despatch of the Draft Report, the Final Report will be issued.
The Final Report will include the information and data required by current internationally recognised regulations. The Final Report, digitally signed or with handwritten signatures, will be issued as PDF file, searchable, bookmarked and hyperlinked, fully compliant with the standard PDF/A-1b (ISO 19005-1 Level B), suitable for long term archiving of electronic document.

7.4 Corrections or additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the Final Report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations. Prior to final archiving of the study data, a full list will be prepared of all records associated with the study.
A reserve sample of each batch of the test item will be taken and kept under the storage conditions of the bulk supply at ERBC. The reserve sample(s) of the test item will be retained within ERBC archives for a period of 10 years and then destroyed.
Any biological samples obtained for analytical measurements or similar determinations will be managed as indicated by the Sponsor in the Draft Report Approval Form or otherwise destroyed at no charge within 3 months from the issue of the Final Report.

The Final Protocol, the Final Report and electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower, where used) will be archived at ERBC.

All other specimens, raw data, records and documentation generated during the course of this study will be archived at ERBC for a period of 3 years, after which the Sponsor will be contacted for shipment or disposal of the material (expenses will be charged to the Sponsor).

9. STUDY CONDUCT

9.1 Language

English and Italian renderings of chemical names, including that of the test material will be considered to be equivalent.

9.2 Scientific decisions

The procedures described in this Protocol may not comprehensively cover all the circumstances that can arise in the assay of the test items. When the study director considers it advisable to modify the procedures described for the selection of a solvent, interpretation of the outcome of the study or other aspects of the study conduct, he/she will carefully record the decision he/she has reached and the reasoning which led to it.

9.3 Quality assurance

According to the ERBC quality assurance programme, defined in the ERBC QA SOPs, this study will be subjected to the following procedures:

- the Protocol will be inspected,
- study/process based inspections of procedures/facilities will be carried out at intervals adequate to assure the integrity of the study,
- the Report will be inspected to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to Management and Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's Representative and Regulatory Authorities.

10. RESPONSIBILITIES OF THE SPONSOR

Items which are the responsibility of the Sponsor are indicated in section 2 of this Protocol. Since full compliance with regulatory requirements may depend on the performance of these items, the Sponsor should ensure that appropriate actions are initiated or undertaken.

11. REFERENCES

United Nations (UN) (2005). Globally Harmonised System of Classification and Labelling of Chemicals (GHS), First revised edition, UN New York and Geneva 2005.

ECVAM Protocol for EPISKIN™: an In Vitro Assay for Assessing Dermal Corrosivity Standard Operating Procedure (October 2000).

ICCVAM Evaluation of EPISKIN™, EpiDerm™ (EPI-200), and the Rat Skin Transcutaneous Electrical Resistance (TER) Assay: In Vitro test methods for Assessing Dermal Corrosivity Potential of Chemicals (NIH Publication No: 02-4502).

INVITTOX Protocol No. 118 EPISKIN™ Skin Corrosivity Test.

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

ERBC S.r.l.

VERIFIED BY : _____ 17-Mar-2021
S. Cinelli, Biol.D., ERT
Associate Scientific Director,
Head of Genetic Toxicology & Alternative Methods
Date

APPROVED BY : _____ 17 March 2021
L. Bisini, Biol.D.
Study Director
Date

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

Aughinish Alumina Ltd.

AUTHORISED BY : _____ 18/03/2021
Date

Name and Title : R. O'Dwyer
Senior Environmental Engeneer

THE
NON-CLINICAL
ENGINE

EUROPEAN RESEARCH BIOLOGY CENTER

Farmed Bauxite Residue, Q4 2019

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL

(EPISKIN™/MTT method)

FINAL REPORT

ERBC STUDY NO. A4246

Sponsor:
Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

COMPLIANCE STATEMENT

I, the undersigned, was responsible for the preparation of this report and hereby declare that it constitutes a true and faithful account of the procedures adopted and of the results obtained in the performance of the study. The aspects of the study conducted by European Research Biology Center S.r.l. were performed in accordance with:

1. Decreto Legislativo 2/3/2007 n. 50, Attuazione delle direttive 2004/9/CE e 2004/10/CE, concernenti l'ispezione e la verifica della Buona Pratica di Laboratorio (BPL) ed il ravvicinamento delle disposizioni legislative, regolamentari ed amministrative relative all'applicazione dei principi di Buona Pratica di Laboratorio ed al controllo della loro applicazione per le prove sulle sostanze chimiche (G.U. 13/4/2007, Serie generale n. 86) and subsequent revisions.
2. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004, on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances.
3. ENV/MC/CHEM(98)17 OECD principles on Good Laboratory Practice (as revised in 1997).

DIGITAL SIGNATURE

L. Bisini, Biol.D.
STUDY DIRECTOR

Date

KEY STUDY STAFF

L. Bisini	Study Director
R. Zanier	Head of Quality Assurance
S. Cinelli	Associate Scientific Director, Head of Genetic Toxicology & Alternative Methods

Test Facility Management

S. Venturella, Biol.D., ERT	Test Facility Director

QUALITY ASSURANCE STATEMENT

Study phases	Inspection dates	Report to SD[a]	Report to CM[b]
Study Plan			
Study Plan check	11.02.2021	15.02.2021	15.02.2021
Study Plan Amendment 1 check	18.03.2021	18.03.2021	18.03.2021
Process based inspections related to this type of study			
Dose preparation	18.01.2021	-	03.03.2021
Treatment	18.03.2021	-	19.03.2021
Final Report (end of review)	*date of QA Statement signature*		

[a] *SD = Study Director only for protocol check and study based inspections*
[b] *CM = Company Management*

Other QA process based inspections were carried out on departments or laboratories performing routine activities (e.g. Analytical Chemistry, Histopathology, Veterinary Services and Clinical Pathology) as well as on other routine activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here. Involved departments or laboratories and support functions are also subject to regular facility inspections.

Review of this report by ERBC QA found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.



7th September 2021

R. Zanier, CMB, Ph.D.
HEAD OF QA

Date

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1 SUMMARY

The potential of the test item Farmed Bauxite Residue, Q4 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™. The experimental procedures are based on the OECD Guideline for testing of chemicals no. 431. The test item, as well as controls, were tested for their ability to impair cell viability after an exposure period of 3, 60±5 and 240±5 minutes. The final endpoint of the assay is the colorimetric measurement of MTT reduction (blue formazan salt) in the test system, being this reaction an index of cell viability. The test item was tested as supplied by the Sponsor.

A preliminary test was carried out to evaluate the compatibility of the test item with the test system. In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Therefore, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

In the Main Assay, for each treatment time, the test item (physical state: solid) was applied as supplied in two replicates, at the treatment level of 20±2 mg/*epidermis* unit, each measuring 0.38 cm^2 (treatment level: 52.6 mg/cm^2). Positive and negative controls (Glacial acetic acid and Physiological saline, respectively) were concurrently tested, in the same number of replicates and test conditions at the treatment level of 50 µL/*epidermis* unit. Positive control was included only at the longest treatment time of 240 minutes, while a negative control was included for each treatment time.

In the Main Assay, the negative controls gave the expected baseline value (Optical Density values ≥ 0.6 and ≤ 1.5) and variability (difference of viability between the two replicates lower than 30%), at each treatment time, in agreement with the guideline indications. For each treatment time, the concurrent negative control mean value is considered the baseline value of the treatment series and thus represents 100% of cell viability.

The positive control caused the expected cell death (0% of cell viability, when compared to the negative control).

Based on the stated criteria, the assay was regarded as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the concurrent blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	120
60	91
240	51

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

2 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the potential skin corrosion of the test item as measured by its ability to induce cell death in a commercial reconstructed human epidermis (RhE) model, EPISKIN™.

2.2 Regulatory compliance

Experimental procedures were based on the following guideline:

- OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method" (Adopted on 18 June 2019).

The Sponsor affirmed that the test item is a chemical product (industrial waste) and that the study was performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

2.3 Principle of the test

The test system EPISKIN™ is a reconstructed human epidermis (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.*, the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue; CAS N. 298-93-1] into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2.4 Sponsor and Test Facility

The study was performed at:

European Research Biology Center S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

On behalf of the Sponsor:

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

2.5 Study schedule

Procedure	**Date**
Protocol approved by: Study Director	09 February 2021
Start of experimental phase Preliminary test	11 February 2021
End of experimental phase Completion of scoring of Main Assay	19 March 2021
Study completion	Date of Study Director's signature on this report

3 TEST ITEM AND CONTROL ITEMS

3.1 Test Item

3.1.1 Identity

Details of the test item received at ERBC were as follows:

Identity	Farmed Bauxite Residue, Q4 2019
Label name	Farmed Bauxite Residue
Batch no.	Q4 2019
Expiry date	January 2022
Storage conditions	Room temperature
ERBC no.	17296

The determination of the identity, strength, purity, composition and stability of the test item and the quality system under which the test item characterisation was performed was the responsibility of the Sponsor. The certificate of analysis is presented in Addendum 1 of this report. A sample of test item was taken and will be stored in the archives of ERBC for 10 years prior to disposal.

3.2 Control Items

Positive control item was Glacial acetic acid (C. Erba, batch no. P8B028018C).

Negative control item was Physiological saline (Baxter, batch no. 19H0603).

Positive and negative control items were obtained commercially and characterised by labelling. Determination of the stability and concentration of solutions of positive and negative controls were not undertaken, since it is sufficient to provide evidence for the correct expected response of the test system to them.

4 METHODS

4.1 Test System

4.1.1 EPISKIN™

Commercial Name	EPISKIN™ - 0.38 cm^2
Supplier	SkinEthic Laboratories (4, A. Fleming – 69366 Lyon – France)
Batch	21-EKIN-011
Arrived at ERBC on	16 March 2021

Functional controls

Quality controls: histology scoring, magnitude of viability and barrier function (IC_{50} determination).

Biological safety: absence of HIV1 and 2 antibodies, hepatitis C antibodies, hepatitis B antigen HBs, absence of bacteria, fungi and mycoplasma.

A certificate of analysis can be found in Addendum 2.

4.1.2 Preparation of the Test System

Examination before use

Temperature indicator: pale grey (suitable for use)

pH indicator: orange (suitable for use)

Preparation and pre-treatment incubation period

At arrival all kit components were maintained at +4°C, until use. According to the supplier procedure, within 24 hours from arrival, plates were opened under a sterile airflow and each insert, containing the epidermal tissue, was carefully taken out and placed in a 12-well plate in which each well had previously been filled with 2 mL/well SkinEthic Maintenance Medium. Culture plates were placed in the incubator at 37°C, 5% CO_2 and saturated humidity for approximately 24 hours.

4.2 Media

Maintenance Medium	SkinEthic; batch: 21-MAIN3-011
Assay Medium	SkinEthic; batches: 21 ESSC 006 and 21 ESSC 011

4.3 Experimental procedure

4.3.1 Preliminary test

Direct MTT reduction test (Step 1)

Non-specific reduction of MTT was evaluated as follows: two mL of MTT ready-to-use solution (0.3 mg/mL) was incubated with 20±2 mg of test item at 37 °C, 5% CO_2 and saturated humidity for 3 hours, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time was carried out.

Colouring potential test (Step 2)

Chemicals' colouring potential was assessed for potential interaction with the test system. 10±1 mg of test item was added to 90 µL of distilled water (Eurospital; batch no. 20C3004) in a transparent tube and the resulting solution/suspension mixed by using a vortex for 15 minutes. Colouring of the solution/suspension at the end of the incubation time was evaluated by unaided eye.

4.3.2 Main Assay

Treatment

In Main Assay, alive tissues were treated with the test item, positive and negative controls. The treatment scheme was the following:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Negative control	Live tissue	Physiological saline	3	50 µL	2	CN1A, CN1B
Negative control	Live tissue	Physiological saline	60	50 µL	2	CN2A, CN2B
Negative control	Live tissue	Physiological saline	240	50 µL	2	CN3A, CN3B
Positive control	Live tissue	Glacial acetic acid	240	50 µL	2	CP1A, CP1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	3	20±2 mg	2	TI-B1A, TI-B1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	60	20±2 mg	2	TI-B2A, TI-B2B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	240	20±2 mg	2	TI-B3A, TI-B3B

Additional controls were included in the Main Assay with the following treatment scheme:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	3	20±2 mg	2	CC-B1A, CC-B1B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	60	20±2 mg	2	CC-B2A, CC-B2B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	240	20±2 mg	2	CC-B3A, CC-B3B

Results presented in this report are obtained in a repeated assay. In the original one, not acceptable negative control values were obtained. Data from the original experiment are not presented in this report but are ratained in the study file and will be archived as indicated in the study protocol.

Exposure period

Exposure times of 3, 60±5 and 240±5 minutes were allowed in a ventilated cabinet at room temperature.

Washing

At the end of the exposure, each tissue was rinsed with approximately 25 mL of sterile PBS, filling and empting the tissue insert. The excess liquid was carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of maintenance medium.

MTT staining

Each tissue insert was incubated with 2 mL/well of MTT ready-to-use solution. Plates were incubated for 3 hours ± 5 minutes at 37°C, 5% CO_2 and saturated humidity. At the end of the incubation period, tissues were placed on absorbent paper to dry. A total biopsy was carried out by means of a biopsy punch to allow biopsies of the same dimensions.

The epidermis were separated from the collagen matrix and both placed in a microtube prefilled with 500 µL of acidic isopropanol. Tubes were mixed by vortexing and preserved overnight at room temperature to allow formazan extraction. At the end of the extraction period, debris were eliminated by short centrifugation of the tubes (14000 rpm for 2 minutes) and aliquots of 200 µL from each sample were read in duplicate for their absorbance at 595 nm. Six aliquots (200 µL) of acidic isopropanol were analysed and used as blank. An MTT formazan calibration curve was performed in order to ensure that OD values obtained in the main experiment were within the spectrophotometer linear range.

4.4 Analysis and evaluation of data

4.4.1 Study Acceptability Criteria

The assay was considered valid if the following criteria were met:

- Blank controls: mean OD value < 0.1.
- Negative controls: mean OD value ≥ 0.6 and ≤ 1.5.
- Positive controls: mean viability expressed as percentage of the negative control ≤ 20%.
- In the range of 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

4.4.2 Interpretation of results and classification

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, mean relative viability values (percentage relative to the concurrent negative control) were calculated.
Cut-off values for the endpoint of the test are established as follows:

Criteria	Classification
< 35% after 3 min exposure	Corrosive Sub-categoria 1A
≥ 35% after 3 min exposure AND < 35% after 60 min exposure OR ≥ 35% after 60 min exposure AND < 35% after 240 min exposure	Corrosive: combination of sub-categories 1B and 1C
≥ 35% after 240 min exposure	Non- Corrosive

For colouring test items, Non Specific Colour (NSC_{living}) relative to the D-PBS Control is evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{test\ item(not\ incubated\ with\ MTT)}}{OD_{negative\ control\ living\ tissues}}$$

If the $NSC_{living} \leq 5\%$ only blank subtraction is carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction is carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

4.5 Protocol deviations

No deviation occurred during the study.

4.6 Archives

Full records of all aspects of the study conduct were maintained together with the results of all measurements and observations. All specimens, raw data, records and documentation generated during the course of this study will be retained within ERBC archives. The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. The Final Protocol, the Final Report and, where applicable, electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower), will be archived at ERBC.

5 RESULTS

5.1 Preliminary test

Before the Main Assay, a preliminary test was carried out to evaluate the compatibility of the test item with the test system. Results of this preliminary test can be found in Table 1.

In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. Thus no additional controls were added in the main phase for the evaluation of MTT non-specific reduction. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Thus, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

5.2 Main Assay

A Main Assay was performed. Raw data and data elaboration are reported in Table 2.

The mean Optical Density of Blank Controls was 0.036, lower than the maximum acceptable value (0.1). All negative control mean OD values gave the expected baseline value and variability, in agreement with guideline indications. According to the method, each negative control mean value is considered the baseline value for the concurrent treatment series, thus they represent 100% of cell viability.

Positive control results indicated an appropriate cell death with an acceptable relative cell viability (0% of the negative control value).

Based on the stated criteria, the study was accepted as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	120
60	91
240	51

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

6 CONCLUSION

The potential of the test item Farmed Bauxite Residue, Q4 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.

The blank, negative and positive controls gave acceptable results at all treatment times, thus the study was accepted as valid.

The mean cell viability of the test item treated tissues, after the blank subtraction, was higher than 35% at all treatment times. Based on these results, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

7 TABLES

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN^{TM}/MTT method)

STUDY NO.: A4246

PRELIMINARY TEST

Direct MTT reduction test (Step 1)

Test item (mg)	**MTT ready to use solution (mL)**	**Container**	**Incubation condition**	**Colour Observation**
20 ± 2	2.0	well	3 h at 37°C, 100% nominal humidity 5% CO_2	Red/brown suspension, with brow precipitate (no interaction)

Colouring potential test (Step 2)

Test item (mg)	**Water (µL)**	**Container**	**Incubation condition**	**Colour Observation**
10 ± 1	90	Eppendorf tube	15', ambient condition, in agitation	Brown suspension (possible interaction)

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 3 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN1A-1	0.6893	0.6530		0.6874	97.5
	0.0364	CN1A-2	0.7582	0.7219			
	0.0364	CN1B-1	0.7556	0.7193		0.7230	102.5
	0.0363	CN1B-2	0.7631	0.7268			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.705	**Mean**	0.705	100
SD	0.0003	**SD**		0.035			
CV(%)	0.84	**CV(%)**		5.0		**Δ (%)**	5.0

Test Item					
				OD_{TI}	**Viability (%)**
TI-B1A-1	0.8913	0.8550		0.9086	128.8
TI-B1A-2	0.9986	0.9623			
TI-B1B-1	0.9876	0.9513		0.7831	111.0
TI-B1B-2	0.6512	0.6149			
Mean		0.846	**Mean**	0.846	**120**
SD		0.161			
CV(%)		19.1		**Δ (%)**	14.8

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B1A-1	0.0480	0.0117		0.0128	1.8
CC-B1A-2	0.0502	0.0139			
CC-B1B-1	0.0489	0.0126		0.0128	1.8
CC-B1B-2	0.0493	0.0130			
Mean		0.013	**Mean**	0.013	**2**
SD		0.001			
CV(%)		7.1		**Δ (%)**	0.0

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 60 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN2A-1	0.8525	0.8162		0.8404	97.7
	0.0364	CN2A-2	0.9009	0.8646			
	0.0364	CN2B-1	0.9044	0.8681		0.8796	102.3
	0.0363	CN2B-2	0.9275	0.8912			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.860	**Mean**	0.860	100
SD	0.0003	**SD**		0.032			
CV(%)	0.84	**CV(%)**		3.7		**Δ (%)**	4.6

Test Item					
				OD_{TI}	**Viability (%)**
TI-B2A-1	0.7962	0.7599		0.7815	90.9
TI-B2A-2	0.8394	0.8031			
TI-B2B-1	0.8477	0.8114		0.7871	91.5
TI-B2B-2	0.7991	0.7628			
Mean		0.784	**Mean**	0.784	**91**
SD		0.027			
CV(%)		3.4		**Δ (%)**	0.7

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B2A-1	0.0503	0.0140		0.0142	1.6
CC-B2A-2	0.0507	0.0144			
CC-B2B-1	0.0506	0.0143			
CC-B2B-2	0.0525	0.0162		0.0152	1.8
Mean		0.015	**Mean**	0.015	**2**
SD		0.001			
CV(%)		6.8		**Δ (%)**	7.1

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582	111.2
	0.0364	CN3A-2	1.0535	1.0172			
	0.0364	CN3B-1	0.9424	0.9061		0.8453	88.8
	0.0363	CN3B-2	0.8208	0.7845			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.952	**Mean**	0.952	100
SD	0.0003	**SD**		0.137			
CV(%)	0.84	**CV(%)**		14.4		**Δ (%)**	22.4

Test Item					
				OD_{TI}	**Viability (%)**
TI-B3A-1	0.3804	0.3441		0.4226	44.4
TI-B3A-2	0.5374	0.5011			
TI-B3B-1	0.5771	0.5408		0.5391	56.6
TI-B3B-2	0.5737	0.5374			
Mean		0.481	**Mean**	0.481	**51**
SD		0.093			
CV(%)		19.3		**Δ (%)**	24.2

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B3A-1	0.0505	0.0142		0.0081	0.9
CC-B3A-2	0.0384	0.0021			
CC-B3B-1	0.0382	0.0019		0.0017	0.2
CC-B3B-2	0.0379	0.0016			
Mean		0.005	**Mean**	0.005	**1**
SD		0.006			
CV(%)		125.1		**Δ (%)**	129.7

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582	111.2
	0.0364	CN3A-2	1.0535	1.0172			
	0.0364	CN3B-1	0.9424	0.9061		0.8453	88.8
	0.0363	CN3B-2	0.8208	0.7845			
	0.0361						
	0.0359						
Mean	0.0363	**Mean**		0.952	**Mean**	0.952	100.0
SD	0.0003	**SD**		0.137			
CV(%)	0.84	**CV(%)**		14.4		**Δ (%)**	22.4

Positive control					
				OD_{TI}	**Viability (%)**
CP1A-1	0.0386	0.0023		0.0019	0.2
CP1A-2	0.0379	0.0016			
CP1B-1	0.0382	0.0019		0.0021	0.2
CP1B-2	0.0386	0.0023			
Mean		0.0020	**Mean**	0.002	**0**
SD		0.0003			
CV(%)		16.9		**Δ (%)**	7.47

RUSAL
AUGHINISH

Aughinish Alumina Ltd.
Aughinish Island
Askeaton
Co. Limerick
IRELAND

CERTIFICATE OF ANALYSIS

Sample Type : Farmed bauxite residue
Sample mass : 10g (approx.) per sample
Report Issued : 12/03/2021

Sample	% Moisture	Units	Method
Farmed Bauxite Residue, Q2 2019	27.5	%w/w	ATM047
Farmed Bauxite Residue, Q4 2019	23.0	%w/w	ATM047
Farmed Bauxite Residue, Q1 2020	24.0	%w/w	ATM047
Farmed Bauxite Residue, Q4 2020	21.4	%w/w	ATM047

Jason Clohessy

LABORATORY QUALITY MANAGER
Jason Clohessy

"This report relates only to the items tested and shall not be reproduced except in full and with the approval of the Laboratory of Aughinish Alumina Ltd".

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS

CCE-091-SM D13-S/04

NAME

EpiSkin™ Small / Human Epidermis (SM/13)

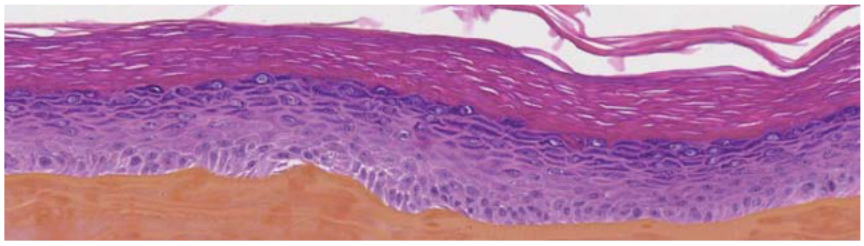
DESCRIPTION

0.38 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on a collagen matrix, for 13 days

BATCH : **21-EKIN-011**
ORIGIN : Adult donors
USAGE : FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN
STORAGE : This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO2 with saturated humidity

QUALITY CONTROLS

Control # E210333

	Process	Specification	Result
HISTOLOGY	HES stained paraffin section	Multi-layered, highly differentiated epidermis consisting of organized basal, spinous and granular layers, and a multilayered *stratum corneum*	**Satisfactory**
		Number of cell layers ≥ 4	**7.5 cell layers**
			
IC50 DETERMINATION	SDS concentration, MTT test.	1.5 mg/mL ≤ IC50 ≤ 3.0 mg/mL	**1.9 mg/mL**

BIOLOGICAL SAFETY:

On blood of the donors, we have verified the absence of HIV1 and 2 antibodies, hepatitis C antibodies and hepatitis B antigen HBs.
On cells from the donors, we have verified the absence of bacteria, fungus and mycoplasma.

SUGGESTED EXPIRATION DATE:

March 22, 2021

Lyon, March 16, 2021
Certified and released by Michel BATAILLON, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

The use of this human tissue is strictly limited to *in vitro* testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

THE
NON-CLINICAL
ENGINE
EUROPEAN RESEARCH BIOLOGY CENTER

Version 20/2

Farmed Bauxite Residue, Q4 2019
***IN VITRO* SKIN CORROSION STUDY USING A**
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

Protocol Amendment 1
prepared for

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

by

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This Protocol Amendment contains changes to the following portions of the original Final Protocol signed on 09 February 2021.
If necessary/applicable, numbering of sections and/or pages may change according to the insertions or deletions applied.
Any changes related to the current amendment are indicated directly in the relevant section/s of the document as follows: any additions are indicated in **bold and underlined** text and any deletions in ~~double strikethrough~~ text. The history of previous changes is indicated below:

Amendment and Section(s)	**Date of issue and Reason for Change**
Amendment 1	**Date of Study Director Signature:** 17 March 2021
Page 6, § 4.1.3 Preparation and storage of the test system	Change of procedure due to organizational problems

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

MANAGEMENT OF STUDY

Study Director	:	L. Bisini, Biol.D. lbisini@erbc-group.com
Sponsor	:	Aughinish Alumina Ltd. Aughinish island, Askeaton Co. Limerick Ireland
Monitor	:	R. O'Dwyer

QUALITY ASSURANCE

Head of QA & GXP Compliance	:	R. Zanier, CMB, Ph.D.

LOCATION OF STUDY

The study will be performed at	:	European Research Biology Center S.r.l. Via Tito Speri, 12/14 00071 Pomezia Italy

The laboratory facilities, archives and administration are located at this site.

PROJECTED TIME PLAN

			Date
1.	Proposed experimental starting date	:	First half of February 2021
2.	Proposed experimental completion date	:	2 weeks from the start of the experimental phase
3.	QA-Audited Draft Report to Sponsor	:	2 weeks after the end of the experimental phase

Any change in the experimental design or any additional activity requested to maintain the scientific or regulatory integrity of the study might cause a change in time schedule indicated above.

1. INTRODUCTION

1.1 Objective

This test allows the identification of non-corrosive and corrosive substances and mixtures in accordance with the UN GHS (1). The test system EPISKIN™ is one of the available commercial reconstructed human *epidermis* (RhE) models used for distinguishing corrosive (C) from non-corrosive (NC) substances. It further supports the sub-categorization of corrosive substances and mixtures into optional Sub-category 1A, in accordance with the UN GHS, as well as a combination of Sub-categories 1B and 1C.

1.2 Regulatory requirements

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 50 of 2 March 2007 and subsequent revisions.

The Sponsor has affirmed that the test item is a chemical product (industrial waste) and that the study will be performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

In addition, the study is designed to comply with the experimental methods indicated in the guidelines of:

OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (Rhe) Test Method" (Adopted on 18 June 2019);

1.3 Principles of the method

The test system EPISKIN™ is a reconstructed human *epidermis* (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.,* the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue], into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item and the quality system under which the test item characterisation was performed will also be the Sponsor's responsibility.
A certificate of analysis for the test item should be supplied.

2.2 Identity

The test item will be Farmed Bauxite Residue, Q4 2019.

The following information, supplied by the Sponsor, refers to the original batch of test item received for the study:

Batch number: Q4 2019
Expiry date: not available
Storage conditions: room temperature

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used will be recorded according to standard procedures.

2.3 Preparation of test item

Test item will be used in the form supplied.
If necessary, solid substances will be ground to reduce particle size and aid suspension.

2.4 Safety precautions

The precautions necessary when handling the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under ERBC Hazard Classification System, according to ERBC standard procedures.

2.5 Disposal

Approximately 1 year after the Final Report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration or returned to the Sponsor.

3. CONTROL ITEMS

3.1 The control items are commercially obtained by ERBC. Information about the identity, strength, purity and composition or other characteristics appropriately defining these compounds, before their use in the study, as well as the stability are detailed in documents obtained from the Supplier.

3.2 Control items will be the following:
- Negative control: The preferred choice will be 0.9% (w/v) NaCl, but Distilled Water (Bieffe Medital or equivalent) can be used, if necessary.
- Positive control item: Glacial Acetic Acid.

Determination of the stability and concentration of solutions of these agents will not be undertaken since it is sufficient to provide evidence of the correct expected response of the test system to them.

4. MATERIALS AND METHODS

4.1 EPISKIN™

The test system EPISKIN™ is commercially available from SkinEthic Laboratories.

4.1.1 Characteristic of the test system

The SkinEthic reconstructed human tissue model EPISKIN™ consists of an airlifted, living, multi-layered tissue construct, produced in polycarbonate inserts in serum-free and chemically defined medium, featuring normal ultra-structure and functionality equivalent to human tissue *in vivo*.
Normal human keratinocytes are used to reconstruct the epithelium. Multiple layers of viable epithelial cells (basal layer, *stratum spinosum, stratum granulosum*) should be present under a functional *stratum corneum*. *Stratum corneum* should be multilayered containing the essential lipid profile to produce a functional barrier with robustness to resist rapid penetration of cytotoxic marker chemicals.

4.1.2 Functional conditions

The barrier function should be demonstrated. The containment properties of the RhE model should prevent the passage of material around the *stratum corneum* to the viable tissue, which would lead to poor modelling of skin exposure.
The RhE model supplier should ensure that each batch of the RhE model used meets defined production release criteria. A certificate will be supplied for each batch of the test system.

4.1.3 Preparation and storage of the test system

Within 24 hours from arrival ~~**Immediately after arrival**~~, the multiwell plate will be opened under a sterile airflow. Each insert containing the epidermal tissue will be carefully taken out. Any remaining agarose that adheres to the outer sides of the insert will be rapidly removed by gentle blotting on the sterile filter paper. Inserts will be quickly placed in a 12-well plate in which each well has previously been filled with 2 mL/well SkinEthic Maintenance Medium (pre-warmed at 37 °C) making sure that no air bubbles are formed underneath the inserts.
Culture plates will be placed in the incubator at 37°C, 5% CO_2 and saturated humidity.

Testing can initiate after at least two hours of incubation.

4.2 Media and reagents

SkinEthic Maintenance Medium Supplied with the EPISKIN™
To be stored at 2-8°C. To be used at room temperature (without pre-heating).

SkinEthic Assay Medium To be stored at 2-8°C.	Supplied with the EPISKIN™
0.9% (w/v) NaCl	
Glacial Acetic Acid	
MTT Stock Solution	3 mg/mL MTT in D-PBS.
MTT Ready-to-use Solution	MTT Stock Solution diluted 1:10 (v/v) with pre-warmed SkinEthic Assay Medium (final concentration 0.3 mg/mL of MTT).
Acidic Isopropanol	0.04 N HCl in Isopropanol
Water-killed epidermis	to be prepared only for MTT interacting reagents. Living epidermis is incubated with 2 mL of distilled water at 37°C, 5% CO_2 and saturated humidity for approximately 2 days. The water is discarded and the samples frozen at -18 to -20°C for up to 6 months.

5. EXPERIMENTAL PROCEDURE

5.1 Experimental design

Before testing the test item for corrosive properties, adequacy of the test system will be verified to ensure that the test item enters in the applicability domain of the assay.
A preliminary test will be undertaken in two steps. The test item will be checked for the ability to reduce the MTT (Step 1) and to colour water (Step 2).
The main experiment will be carried out including all controls to assess corrosive potential and classify the test item, according to the EU/GHS regulations.

5.2 Preliminary test

5.2.1 Direct MTT reduction test (Step 1)

Non-specific reduction of MTT will be evaluated as follows:
Two mL of MTT Ready-to-use Solution will be incubated with an amount of the test item (50 µL if liquid, 20 ± 2 mg if solid) and incubated at 37°C, 5% CO_2 and saturated humidity for 3 hours protected from light, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time will imply the use of water killed epidermis as a control in the main assay (additional cost).

5.2.2 Colouring potential test (Step 2)

To identify potential interference by coloured test chemicals or test chemicals that become coloured when in contact with water and decide on the need for additional controls, spectral analysis of the test chemical in water should be performed.
An amount of the test item (10 µL if liquid, 10 ± 1 mg if solid) will be added to 90 µL of distilled water in a transparent tube (vial or micro-tube). The mixture will be blended for approximately 15 minutes and spectral analysis, if necessary, will be performed at 595 nm.
Colouring of the solution (e.g. observation of blue or purple appearance) at the end of the incubation time will imply the use of alive samples treated without MTT as a control in the main assay.

5.2.3 Further preliminary test (Additional cost)

When a positive result is obtained in preliminary tests described either in section 5.2.1 or 5.2.2 (or both), further preliminary test may be conducted to quantify the ability of the test item to reduce MTT or to stain tissue before beginning the main test. The results may indicate that the test item is not suitable for the test system before beginning a complete main assay. These assays will be conducted only in agreement with the Sponsor.
Otherwise, the Main Assay will be conducted with all the appropriate controls.

5.3 Main Assay

5.3.1 Treatment scheme

A Main Assay will be carried out including the test item, positive and negative controls. A typical treatment scheme may be the following:

Basic assay:

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Negative control 1	Live tissue	0.9% NaCl or distilled water	3	2
Negative control 2	Live tissue		60 (± 5)	2
Negative control 3	Live tissue		240 (± 5)	2
Positive control	Live tissue	Glacial acetic acid	240 (± 5)	2
Test item 1	Live tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item 2	Live tissue		60 (± 5)	2
Test item 3	Live tissue		240 (± 5)	2

Additional controls

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Test item 1 *	Killed tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item 2 *			60 (± 5)	2
Test item 3 *			240 (± 5)	2
Negative control 1 *	Killed tissue	0.9% NaCl or distilled water	3	2
Negative control 2 *			60 (± 5)	2
Negative control 3 *			240 (± 5)	2
Test item without MTT 1 §	Killed tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item without MTT 2 §			60 (± 5)	2
Test item without MTT 3 §			240 (± 5)	2
Test item without MTT 1 °	Live tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item without MTT 2 °			60 (± 5)	2
Test item without MTT 3°			240 (± 5)	2

* to be added in case of test items able to reduce MTT (killed tissue will be of the same batch but the batch will be different from the alive tissue batch).
° to be added in case of test items able to stain tissue or with a potential to stain tissue.
§ to be added in case of test items able both to stain tissue and reduce MTT.

Additional experiments could be performed if necessary.

5.3.2 Treatment procedure

A sufficient amount of the test or control item (50 ± 3 µL if liquid, 20 ± 2 mg if solid, 50 ± 2 mg if waxy/sticky) will be applied to uniformely cover each epidermis surface while avoiding an infinite dose. This will allow a surface exposure of approximately 131.6 µL or mg/cm^2 (liquid or waxy/stixy substances) or 52.6 mg/cm^2 (solid substances) being the treatment area of the commercial test system equal to 0.38 cm^2. Only for solid chemicals, the epidermis surface will be moistened with 100 ± 5 µL of 0.9% NaCl solution after application of the test item. Waxy/sticky test items will be added on each single tissue with a nylon mesh, if necessary.
The exposure time will be allowed in a ventilated cabinet at room temperature. For peculiar test items (e.g. surfactant and viscous liquids), an intermediate re-spreading will be carried out, if necessary.
Each tissue will then be rinsed with approximately 25 mL of sterile PBS filling and empting the tissue insert. The excess liquid will be carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of pre-warmed maintenance medium.

5.3.3 MTT Assay

The tissue inserts and controls will be incubated with 2 mL/well of MTT ready to use solution with the exception of treated tissues without MTT which will be incubated with SkinEthic Maintenance Medium.

Plates will be incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity.
At the end of the incubation period, tissues will be placed on absorbent paper to dry. A total biopsy will be carried out by means of a specific biopsy punch supplied by SkinEthic to allow biopsies of the same dimensions. The epidermis will be separated from the collagen matrix and will both be placed in a microtube prefilled with 500 µl of acidic isopropanol. In the case of coloured collagen, unstained and untreated collagen matrices taken from killed epidermis may substitute the coloured collagen.
Tubes will be mixed by vortexing and preserved overnight at room temperature to allow formazan extraction.
At the end of the extraction period, debris will be eliminated by short centrifugation of the tubes (e.g. at 10000-14000 rpm for 2 minutes).
Aliquots of 200 µl from each sample will be read in duplicate for their absorbance at 595 nm. Optical Density (OD) values will be recorded.
On the day of the analysis, the spectrophotometer will be verified against standard solutions of MTT formazan prepared in acidic isopropanol, in order to verify if the OD values fall in the linearity range of the spectrophotometer.

5.3.4 Special procedures for control wells

Control for potentially tissue-staining test items (killed/alive epidermis)
SkinEthic Assay Medium will be added to the test item-treated well instead of MTT solution. All other procedures will be carried out as described for the main assay.

Water killed epidermis control
Before use, tissues will be thawed by incubation at room temperature with 2 mL of SkinEthic Maintenance Medium for at least one hour. All other procedures will be carried out as described for the Main Assay.

6. EVALUATION OF RESULTS

6.1 Study acceptability criteria

Blank controls: mean OD value < 0.1
Negative controls (for each exposure time point): mean OD value ≥ 0.6 and ≤ 1.5
Positive controls: mean viability expressed as percentage of the negative control ≤ 20%
Intra-replicate variability: in the range 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

6.2 Interpretation of results and classification as corrosive

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, relative and mean relative viability values (percentage relative to the negative control) will be calculated.

Cut-off values for the endpoint of the test are established as follows:

Viability related to concurrent negative control	Classification
< 35% after 3 min exposure	**Corrosive:** • Sub-categoria 1A (optional)
≥ 35% after 3 min exposure **AND** < 35% after 60 min exposure **OR** ≥ 35% after 60 min exposure **AND** < 35% after 240 min exposure	**Corrosive:** • A combination of sub-categories 1B and 1C (optional)
≥ 35% after 240 min exposure	**Non-corrosive**

For direct MTT interacting test items, non specific MTT reduction calculation (NSMTT) relative to the Negative Control will be evaluated as follows:

$$NSMTT = 100 \times \frac{OD_{\text{treated killed tissues}} - OD_{\text{non-treated killed tissues}}}{OD_{\text{negative control living tissues}}}$$

The NSMTT control per exposure time will be performed concurrently to the testing of the coloured test item.
If the NSMTT ≤ 5% only blank subtraction will be carried out.
If 5% < NSMTT ≤ 50% blank and appropriate background subtraction will be carried out.
If NSMTT > 50% results should be taken with caution.

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control will be evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{\text{test item (not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

The NSC_{living} control per exposure time will be performed concurrently to the testing of the coloured test item and in case of multiple testing, an independent NSC control will be conducted with each test performed (in each run).
If the $NSC_{living} \leq 5\%$ only blank subtraction will be carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction will be carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

For test items able both to stain tissue and reduce MTT, to avoid a possible double correction for colour interference, a third control for Non Specific Colour in killed tissues (NSC_{killed}) will be evaluated per exposure time:

$$NSC_{killed} = 100 \times \frac{OD_{\text{test item (treated killed tissues not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

If the $[(NSMTT + NSC_{living}) - NSC_{killed}] \leq 5\%$ this value will not be considered for the final calculation.

If 5% < [(NSMTT + NSC_{living}) - NSC_{killed}] ≤ 50% blank subtraction and appropriate background subtraction will be carried out.
If [(NSMTT + NSC_{living}) - NSC_{killed}] > 50% results should be taken with caution.

A single NSC_{killed} control is sufficient per test item regardless of the number of independent tests/runs performed, but should be performed concurrently to the NSMTT control.

The above corrections should be applied when the mean OD value of test item treated tissues without any correction is within the linearity range of the spectrophotometer. In case of strong interference (OD values out of the linear range) the test item is not suitable for this test method.

7. REPORTING

7.1 Presentation of data

The results will be presented in the form of tables.

7.2 Interim Report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.3 Final Report

A Draft Report will be sent to the Sponsor together with the Draft Report Approval Form. With the exception of signatures, the Draft Report will contain all information and data included in the Final Report.
Comments made by the Sponsor may be incorporated and the Final Report will be issued. If comments are not received within 6 months from despatch of the Draft Report, the Final Report will be issued.
The Final Report will include the information and data required by current internationally recognised regulations. The Final Report, digitally signed or with handwritten signatures, will be issued as PDF file, searchable, bookmarked and hyperlinked, fully compliant with the standard PDF/A-1b (ISO 19005-1 Level B), suitable for long term archiving of electronic document.

7.4 Corrections or additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the Final Report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations. Prior to final archiving of the study data, a full list will be prepared of all records associated with the study.
A reserve sample of each batch of the test item will be taken and kept under the storage conditions of the bulk supply at ERBC. The reserve sample(s) of the test item will be retained within ERBC archives for a period of 10 years and then destroyed.

Any biological samples obtained for analytical measurements or similar determinations will be managed as indicated by the Sponsor in the Draft Report Approval Form or otherwise destroyed at no charge within 3 months from the issue of the Final Report.

The Final Protocol, the Final Report and electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower, where used) will be archived at ERBC.

All other specimens, raw data, records and documentation generated during the course of this study will be archived at ERBC for a period of 3 years, after which the Sponsor will be contacted for shipment or disposal of the material (expenses will be charged to the Sponsor).

9. STUDY CONDUCT

9.1 Language

English and Italian renderings of chemical names, including that of the test material will be considered to be equivalent.

9.2 Scientific decisions

The procedures described in this Protocol may not comprehensively cover all the circumstances that can arise in the assay of the test items. When the study director considers it advisable to modify the procedures described for the selection of a solvent, interpretation of the outcome of the study or other aspects of the study conduct, he/she will carefully record the decision he/she has reached and the reasoning which led to it.

9.3 Quality assurance

According to the ERBC quality assurance programme, defined in the ERBC QA SOPs, this study will be subjected to the following procedures:

- the Protocol will be inspected,
- study/process based inspections of procedures/facilities will be carried out at intervals adequate to assure the integrity of the study,
- the Report will be inspected to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to Management and Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's Representative and Regulatory Authorities.

10. RESPONSIBILITIES OF THE SPONSOR

Items which are the responsibility of the Sponsor are indicated in section 2 of this Protocol. Since full compliance with regulatory requirements may depend on the performance of these items, the Sponsor should ensure that appropriate actions are initiated or undertaken.

11. REFERENCES

United Nations (UN) (2005). Globally Harmonised System of Classification and Labelling of Chemicals (GHS), First revised edition, UN New York and Geneva 2005.

ECVAM Protocol for EPISKIN™: an In Vitro Assay for Assessing Dermal Corrosivity Standard Operating Procedure (October 2000).

ICCVAM Evaluation of EPISKIN™, EpiDerm™ (EPI-200), and the Rat Skin Transcutaneous Electrical Resistance (TER) Assay: In Vitro test methods for Assessing Dermal Corrosivity Potential of Chemicals (NIH Publication No: 02-4502).

INVITTOX Protocol No. 118 EPISKIN™ Skin Corrosivity Test.

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

ERBC S.r.l.

VERIFIED BY : _____ 17-Mar-2021
S. Cinelli, Biol.D., ERT — Date
Associate Scientific Director,
Head of Genetic Toxicology & Alternative Methods

APPROVED BY : _____ 17 Mar 2021
L. Bisini, Biol.D. — Date
Study Director

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

Aughinish Alumina Ltd.

AUTHORISED BY : _____ 18/03/2021.
Date

Name and Title : R. O'Dwyer
Senior Environmental Engeneer

THE
NON-CLINICAL
ENGINE

EUROPEAN RESEARCH BIOLOGY CENTER

Farmed Bauxite Residue, Q4 2019

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL

(EPISKIN™/MTT method)

FINAL REPORT

ERBC STUDY NO. A4246

Sponsor:
Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

COMPLIANCE STATEMENT

I, the undersigned, was responsible for the preparation of this report and hereby declare that it constitutes a true and faithful account of the procedures adopted and of the results obtained in the performance of the study. The aspects of the study conducted by European Research Biology Center S.r.l. were performed in accordance with:

1. Decreto Legislativo 2/3/2007 n. 50, Attuazione delle direttive 2004/9/CE e 2004/10/CE, concernenti l'ispezione e la verifica della Buona Pratica di Laboratorio (BPL) ed il ravvicinamento delle disposizioni legislative, regolamentari ed amministrative relative all'applicazione dei principi di Buona Pratica di Laboratorio ed al controllo della loro applicazione per le prove sulle sostanze chimiche (G.U. 13/4/2007, Serie generale n. 86) and subsequent revisions.
2. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004, on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances.
3. ENV/MC/CHEM(98)17 OECD principles on Good Laboratory Practice (as revised in 1997).

DIGITAL SIGNATURE

L. Bisini, Biol.D.
STUDY DIRECTOR

Date

KEY STUDY STAFF

L. Bisini	Study Director
R. Zanier	Head of Quality Assurance
S. Cinelli	Associate Scientific Director, Head of Genetic Toxicology & Alternative Methods

Test Facility Management

S. Venturella, Biol.D., ERT	Test Facility Director

QUALITY ASSURANCE STATEMENT

Study phases	Inspection dates	Report to SD[a]	Report to CM[b]
Study Plan			
Study Plan check	11.02.2021	15.02.2021	15.02.2021
Study Plan Amendment 1 check	18.03.2021	18.03.2021	18.03.2021
Process based inspections related to this type of study			
Dose preparation	18.01.2021	-	03.03.2021
Treatment	18.03.2021	-	19.03.2021
Final Report (end of review)	*date of QA Statement signature*		

[a] *SD = Study Director only for protocol check and study based inspections*
[b] *CM = Company Management*

Other QA process based inspections were carried out on departments or laboratories performing routine activities (e.g. Analytical Chemistry, Histopathology, Veterinary Services and Clinical Pathology) as well as on other routine activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here. Involved departments or laboratories and support functions are also subject to regular facility inspections.

Review of this report by ERBC QA found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.



7th September 2021

R. Zanier, CMB, Ph.D.
HEAD OF QA

Date

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1 SUMMARY

The potential of the test item Farmed Bauxite Residue, Q4 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™. The experimental procedures are based on the OECD Guideline for testing of chemicals no. 431. The test item, as well as controls, were tested for their ability to impair cell viability after an exposure period of 3, 60±5 and 240±5 minutes. The final endpoint of the assay is the colorimetric measurement of MTT reduction (blue formazan salt) in the test system, being this reaction an index of cell viability. The test item was tested as supplied by the Sponsor.

A preliminary test was carried out to evaluate the compatibility of the test item with the test system. In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Therefore, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

In the Main Assay, for each treatment time, the test item (physical state: solid) was applied as supplied in two replicates, at the treatment level of 20±2 mg/*epidermis* unit, each measuring 0.38 cm^2 (treatment level: 52.6 mg/cm^2). Positive and negative controls (Glacial acetic acid and Physiological saline, respectively) were concurrently tested, in the same number of replicates and test conditions at the treatment level of 50 µL/*epidermis* unit. Positive control was included only at the longest treatment time of 240 minutes, while a negative control was included for each treatment time.

In the Main Assay, the negative controls gave the expected baseline value (Optical Density values ≥ 0.6 and ≤ 1.5) and variability (difference of viability between the two replicates lower than 30%), at each treatment time, in agreement with the guideline indications. For each treatment time, the concurrent negative control mean value is considered the baseline value of the treatment series and thus represents 100% of cell viability.

The positive control caused the expected cell death (0% of cell viability, when compared to the negative control).

Based on the stated criteria, the assay was regarded as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the concurrent blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	120
60	91
240	51

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

2 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the potential skin corrosion of the test item as measured by its ability to induce cell death in a commercial reconstructed human epidermis (RhE) model, EPISKIN™.

2.2 Regulatory compliance

Experimental procedures were based on the following guideline:

- OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method" (Adopted on 18 June 2019).

The Sponsor affirmed that the test item is a chemical product (industrial waste) and that the study was performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

2.3 Principle of the test

The test system EPISKIN™ is a reconstructed human epidermis (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.*, the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue; CAS N. 298-93-1] into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2.4 Sponsor and Test Facility

The study was performed at:

European Research Biology Center S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

On behalf of the Sponsor:

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

2.5 Study schedule

Procedure	**Date**
Protocol approved by: Study Director	09 February 2021
Start of experimental phase Preliminary test	11 February 2021
End of experimental phase Completion of scoring of Main Assay	19 March 2021
Study completion	Date of Study Director's signature on this report

3 TEST ITEM AND CONTROL ITEMS

3.1 Test Item

3.1.1 Identity

Details of the test item received at ERBC were as follows:

Identity	Farmed Bauxite Residue, Q4 2019
Label name	Farmed Bauxite Residue
Batch no.	Q4 2019
Expiry date	January 2022
Storage conditions	Room temperature
ERBC no.	17296

The determination of the identity, strength, purity, composition and stability of the test item and the quality system under which the test item characterisation was performed was the responsibility of the Sponsor. The certificate of analysis is presented in Addendum 1 of this report. A sample of test item was taken and will be stored in the archives of ERBC for 10 years prior to disposal.

3.2 Control Items

Positive control item was Glacial acetic acid (C. Erba, batch no. P8B028018C).

Negative control item was Physiological saline (Baxter, batch no. 19H0603).

Positive and negative control items were obtained commercially and characterised by labelling. Determination of the stability and concentration of solutions of positive and negative controls were not undertaken, since it is sufficient to provide evidence for the correct expected response of the test system to them.

4 METHODS

4.1 Test System

4.1.1 EPISKIN™

Commercial Name	EPISKIN™ - 0.38 cm^2
Supplier	SkinEthic Laboratories (4, A. Fleming – 69366 Lyon – France)
Batch	21-EKIN-011
Arrived at ERBC on	16 March 2021

Functional controls

Quality controls: histology scoring, magnitude of viability and barrier function (IC_{50} determination).

Biological safety: absence of HIV1 and 2 antibodies, hepatitis C antibodies, hepatitis B antigen HBs, absence of bacteria, fungi and mycoplasma.

A certificate of analysis can be found in Addendum 2.

4.1.2 Preparation of the Test System

Examination before use

Temperature indicator: pale grey (suitable for use)

pH indicator: orange (suitable for use)

Preparation and pre-treatment incubation period

At arrival all kit components were maintained at +4°C, until use. According to the supplier procedure, within 24 hours from arrival, plates were opened under a sterile airflow and each insert, containing the epidermal tissue, was carefully taken out and placed in a 12-well plate in which each well had previously been filled with 2 mL/well SkinEthic Maintenance Medium. Culture plates were placed in the incubator at 37°C, 5% CO_2 and saturated humidity for approximately 24 hours.

4.2 Media

Maintenance Medium	SkinEthic; batch: 21-MAIN3-011
Assay Medium	SkinEthic; batches: 21 ESSC 006 and 21 ESSC 011

4.3 Experimental procedure

4.3.1 Preliminary test

Direct MTT reduction test (Step 1)

Non-specific reduction of MTT was evaluated as follows: two mL of MTT ready-to-use solution (0.3 mg/mL) was incubated with 20±2 mg of test item at 37 °C, 5% CO_2 and saturated humidity for 3 hours, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time was carried out.

Colouring potential test (Step 2)

Chemicals' colouring potential was assessed for potential interaction with the test system. 10±1 mg of test item was added to 90 µL of distilled water (Eurospital; batch no. 20C3004) in a transparent tube and the resulting solution/suspension mixed by using a vortex for 15 minutes. Colouring of the solution/suspension at the end of the incubation time was evaluated by unaided eye.

4.3.2 Main Assay

Treatment

In Main Assay, alive tissues were treated with the test item, positive and negative controls. The treatment scheme was the following:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Negative control	Live tissue	Physiological saline	3	50 µL	2	CN1A, CN1B
Negative control	Live tissue	Physiological saline	60	50 µL	2	CN2A, CN2B
Negative control	Live tissue	Physiological saline	240	50 µL	2	CN3A, CN3B
Positive control	Live tissue	Glacial acetic acid	240	50 µL	2	CP1A, CP1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	3	20±2 mg	2	TI-B1A, TI-B1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	60	20±2 mg	2	TI-B2A, TI-B2B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2019	240	20±2 mg	2	TI-B3A, TI-B3B

Additional controls were included in the Main Assay with the following treatment scheme:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	3	20±2 mg	2	CC-B1A, CC-B1B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	60	20±2 mg	2	CC-B2A, CC-B2B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2019	240	20±2 mg	2	CC-B3A, CC-B3B

Results presented in this report are obtained in a repeated assay. In the original one, not acceptable negative control values were obtained. Data from the original experiment are not presented in this report but are ratained in the study file and will be archived as indicated in the study protocol.

Exposure period

Exposure times of 3, 60±5 and 240±5 minutes were allowed in a ventilated cabinet at room temperature.

Washing

At the end of the exposure, each tissue was rinsed with approximately 25 mL of sterile PBS, filling and empting the tissue insert. The excess liquid was carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of maintenance medium.

MTT staining

Each tissue insert was incubated with 2 mL/well of MTT ready-to-use solution. Plates were incubated for 3 hours ± 5 minutes at 37°C, 5% CO_2 and saturated humidity. At the end of the incubation period, tissues were placed on absorbent paper to dry. A total biopsy was carried out by means of a biopsy punch to allow biopsies of the same dimensions.

The epidermis were separated from the collagen matrix and both placed in a microtube prefilled with 500 µL of acidic isopropanol. Tubes were mixed by vortexing and preserved overnight at room temperature to allow formazan extraction. At the end of the extraction period, debris were eliminated by short centrifugation of the tubes (14000 rpm for 2 minutes) and aliquots of 200 µL from each sample were read in duplicate for their absorbance at 595 nm. Six aliquots (200 µL) of acidic isopropanol were analysed and used as blank. An MTT formazan calibration curve was performed in order to ensure that OD values obtained in the main experiment were within the spectrophotometer linear range.

4.4 Analysis and evaluation of data

4.4.1 Study Acceptability Criteria

The assay was considered valid if the following criteria were met:

- Blank controls: mean OD value < 0.1.
- Negative controls: mean OD value ≥ 0.6 and ≤ 1.5.
- Positive controls: mean viability expressed as percentage of the negative control ≤ 20%.
- In the range of 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

4.4.2 Interpretation of results and classification

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, mean relative viability values (percentage relative to the concurrent negative control) were calculated.
Cut-off values for the endpoint of the test are established as follows:

Criteria	Classification
< 35% after 3 min exposure	Corrosive Sub-categoria 1A
≥ 35% after 3 min exposure AND < 35% after 60 min exposure OR ≥ 35% after 60 min exposure AND < 35% after 240 min exposure	Corrosive: combination of sub-categories 1B and 1C
≥ 35% after 240 min exposure	Non- Corrosive

For colouring test items, Non Specific Colour (NSC_{living}) relative to the D-PBS Control is evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{test\ item(not\ incubated\ with\ MTT)}}{OD_{negative\ control\ living\ tissues}}$$

If the $NSC_{living} \leq 5\%$ only blank subtraction is carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction is carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

4.5 Protocol deviations

No deviation occurred during the study.

4.6 Archives

Full records of all aspects of the study conduct were maintained together with the results of all measurements and observations. All specimens, raw data, records and documentation generated during the course of this study will be retained within ERBC archives. The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. The Final Protocol, the Final Report and, where applicable, electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower), will be archived at ERBC.

5 RESULTS

5.1 Preliminary test

Before the Main Assay, a preliminary test was carried out to evaluate the compatibility of the test item with the test system. Results of this preliminary test can be found in Table 1.

In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. Thus no additional controls were added in the main phase for the evaluation of MTT non-specific reduction. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Thus, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

5.2 Main Assay

A Main Assay was performed. Raw data and data elaboration are reported in Table 2.

The mean Optical Density of Blank Controls was 0.036, lower than the maximum acceptable value (0.1). All negative control mean OD values gave the expected baseline value and variability, in agreement with guideline indications. According to the method, each negative control mean value is considered the baseline value for the concurrent treatment series, thus they represent 100% of cell viability.

Positive control results indicated an appropriate cell death with an acceptable relative cell viability (0% of the negative control value).

Based on the stated criteria, the study was accepted as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after 240 minutes of treatment with the test item. However, values of mean cell viability were higher than 35% at all treatment times. Each mean cell viability, after the blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	120
60	91
240	51

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

6 CONCLUSION

The potential of the test item Farmed Bauxite Residue, Q4 2019 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.

The blank, negative and positive controls gave acceptable results at all treatment times, thus the study was accepted as valid.

The mean cell viability of the test item treated tissues, after the blank subtraction, was higher than 35% at all treatment times. Based on these results, the test item Farmed Bauxite Residue, Q4 2019 is identified as non-corrosive to the skin.

7 TABLES

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN^{TM}/MTT method)

STUDY NO.: A4246

PRELIMINARY TEST

Direct MTT reduction test (Step 1)

Test item (mg)	**MTT ready to use solution (mL)**	**Container**	**Incubation condition**	**Colour Observation**
20 ± 2	2.0	well	3 h at 37°C, 100% nominal humidity 5% CO_2	Red/brown suspension, with brow precipitate (no interaction)

Colouring potential test (Step 2)

Test item (mg)	**Water (µL)**	**Container**	**Incubation condition**	**Colour Observation**
10 ± 1	90	Eppendorf tube	15', ambient condition, in agitation	Brown suspension (possible interaction)

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 3 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN1A-1	0.6893	0.6530		0.6874	97.5
	0.0364	CN1A-2	0.7582	0.7219			
	0.0364	CN1B-1	0.7556	0.7193		0.7230	102.5
	0.0363	CN1B-2	0.7631	0.7268			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.705	**Mean**	0.705	100
SD	0.0003	**SD**		0.035			
CV(%)	0.84	**CV(%)**		5.0		**Δ (%)**	5.0

Test Item					
				OD_{TI}	**Viability (%)**
TI-B1A-1	0.8913	0.8550		0.9086	128.8
TI-B1A-2	0.9986	0.9623			
TI-B1B-1	0.9876	0.9513		0.7831	111.0
TI-B1B-2	0.6512	0.6149			
Mean		0.846	**Mean**	0.846	**120**
SD		0.161			
CV(%)		19.1		**Δ (%)**	14.8

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B1A-1	0.0480	0.0117		0.0128	1.8
CC-B1A-2	0.0502	0.0139			
CC-B1B-1	0.0489	0.0126		0.0128	1.8
CC-B1B-2	0.0493	0.0130			
Mean		0.013	**Mean**	0.013	**2**
SD		0.001			
CV(%)		7.1		**Δ (%)**	0.0

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 60 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN2A-1	0.8525	0.8162		0.8404	97.7
	0.0364	CN2A-2	0.9009	0.8646			
	0.0364	CN2B-1	0.9044	0.8681		0.8796	102.3
	0.0363	CN2B-2	0.9275	0.8912			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.860	**Mean**	0.860	100
SD	0.0003	**SD**		0.032			
CV(%)	0.84	**CV(%)**		3.7		**Δ (%)**	4.6

Test Item					
				OD_{TI}	**Viability (%)**
TI-B2A-1	0.7962	0.7599		0.7815	90.9
TI-B2A-2	0.8394	0.8031			
TI-B2B-1	0.8477	0.8114		0.7871	91.5
TI-B2B-2	0.7991	0.7628			
Mean		0.784	**Mean**	0.784	**91**
SD		0.027			
CV(%)		3.4		**Δ (%)**	0.7

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B2A-1	0.0503	0.0140		0.0142	1.6
CC-B2A-2	0.0507	0.0144			
CC-B2B-1	0.0506	0.0143			
CC-B2B-2	0.0525	0.0162		0.0152	1.8
Mean		0.015	**Mean**	0.015	**2**
SD		0.001			
CV(%)		6.8		**Δ (%)**	7.1

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582	111.2
	0.0364	CN3A-2	1.0535	1.0172			
	0.0364	CN3B-1	0.9424	0.9061		0.8453	88.8
	0.0363	CN3B-2	0.8208	0.7845			
	0.0361						
	0.0359						
Mean	0.036	**Mean**		0.952	**Mean**	0.952	100
SD	0.0003	**SD**		0.137			
CV(%)	0.84	**CV(%)**		14.4		**Δ (%)**	22.4

Test Item					
				OD_{TI}	**Viability (%)**
TI-B3A-1	0.3804	0.3441		0.4226	44.4
TI-B3A-2	0.5374	0.5011			
TI-B3B-1	0.5771	0.5408		0.5391	56.6
TI-B3B-2	0.5737	0.5374			
Mean		0.481	**Mean**	0.481	**51**
SD		0.093			
CV(%)		19.3		**Δ (%)**	24.2

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B3A-1	0.0505	0.0142		0.0081	0.9
CC-B3A-2	0.0384	0.0021			
CC-B3B-1	0.0382	0.0019		0.0017	0.2
CC-B3B-2	0.0379	0.0016			
Mean		0.005	**Mean**	0.005	**1**
SD		0.006			
CV(%)		125.1		**Δ (%)**	129.7

Farmed Bauxite Residue, Q4 2019
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4246

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0368	CN3A-1	1.1355	1.0992		1.0582	111.2
	0.0364	CN3A-2	1.0535	1.0172			
	0.0364	CN3B-1	0.9424	0.9061		0.8453	88.8
	0.0363	CN3B-2	0.8208	0.7845			
	0.0361						
	0.0359						
Mean	0.0363	**Mean**		0.952	**Mean**	0.952	100.0
SD	0.0003	**SD**		0.137			
CV(%)	0.84	**CV(%)**		14.4		**Δ (%)**	22.4

Positive control					
				OD_{TI}	**Viability (%)**
CP1A-1	0.0386	0.0023		0.0019	0.2
CP1A-2	0.0379	0.0016			
CP1B-1	0.0382	0.0019		0.0021	0.2
CP1B-2	0.0386	0.0023			
Mean		0.0020	**Mean**	0.002	**0**
SD		0.0003			
CV(%)		16.9		**Δ (%)**	7.47

8 ADDENDA

RUSAL
AUGHINISH

Aughinish Alumina Ltd.
Aughinish Island
Askeaton
Co. Limerick
IRELAND

CERTIFICATE OF ANALYSIS

Sample Type : Farmed bauxite residue
Sample mass : 10g (approx.) per sample
Report Issued : 12/03/2021

Sample	% Moisture	Units	Method
Farmed Bauxite Residue, Q2 2019	27.5	%w/w	ATM047
Farmed Bauxite Residue, Q4 2019	23.0	%w/w	ATM047
Farmed Bauxite Residue, Q1 2020	24.0	%w/w	ATM047
Farmed Bauxite Residue, Q4 2020	21.4	%w/w	ATM047

Jason Clohessy

LABORATORY QUALITY MANAGER
Jason Clohessy

"This report relates only to the items tested and shall not be reproduced except in full and with the approval of the Laboratory of Aughinish Alumina Ltd".

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS

CCE-091-SM D13-S/04

NAME

EpiSkin™ Small / Human Epidermis (SM/13)

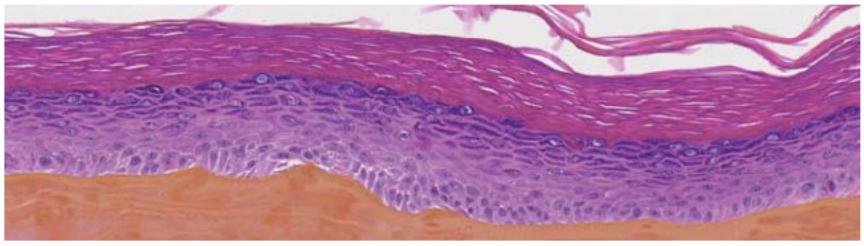
DESCRIPTION

0.38 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on a collagen matrix, for 13 days

BATCH : **21-EKIN-011**
ORIGIN : Adult donors
USAGE : FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN
STORAGE : This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO2 with saturated humidity

QUALITY CONTROLS

Control # E210333

	Process	Specification	Result
HISTOLOGY	HES stained paraffin section	Multi-layered, highly differentiated epidermis consisting of organized basal, spinous and granular layers, and a multilayered *stratum corneum*	**Satisfactory**
		Number of cell layers ≥ 4	**7.5 cell layers**
			
IC50 DETERMINATION	SDS concentration, MTT test.	1.5 mg/mL ≤ IC50 ≤ 3.0 mg/mL	**1.9 mg/mL**

BIOLOGICAL SAFETY:

On blood of the donors, we have verified the absence of HIV1 and 2 antibodies, hepatitis C antibodies and hepatitis B antigen HBs.
On cells from the donors, we have verified the absence of bacteria, fungus and mycoplasma.

SUGGESTED EXPIRATION DATE:

March 22, 2021

Lyon, March 16, 2021
Certified and released by Michel BATAILLON, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

The use of this human tissue is strictly limited to *in vitro* testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

THE
NON-CLINICAL
ENGINE
EUROPEAN RESEARCH BIOLOGY CENTER

Version 20/2

Farmed Bauxite Residue, Q4 2019
***IN VITRO* SKIN CORROSION STUDY USING A**
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

Protocol Amendment 1
prepared for

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

by

EUROPEAN RESEARCH BIOLOGY CENTER S.r.l.
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Società a socio unico soggetta a direzione e coordinamento di ERBC SA, Chemin de Montifault, 18800 Baugy (Francia)
www.erbc-group.com

This Protocol Amendment contains changes to the following portions of the original Final Protocol signed on 09 February 2021.
If necessary/applicable, numbering of sections and/or pages may change according to the insertions or deletions applied.
Any changes related to the current amendment are indicated directly in the relevant section/s of the document as follows: any additions are indicated in **bold and underlined** text and any deletions in ~~double strikethrough~~ text. The history of previous changes is indicated below:

Amendment and Section(s)	**Date of issue and Reason for Change**
Amendment 1	**Date of Study Director Signature:** 17 March 2021
Page 6, § 4.1.3 Preparation and storage of the test system	Change of procedure due to organizational problems

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

MANAGEMENT OF STUDY

Study Director	:	L. Bisini, Biol.D. lbisini@erbc-group.com
Sponsor	:	Aughinish Alumina Ltd. Aughinish island, Askeaton Co. Limerick Ireland
Monitor	:	R. O'Dwyer

QUALITY ASSURANCE

Head of QA & GXP Compliance	:	R. Zanier, CMB, Ph.D.

LOCATION OF STUDY

The study will be performed at	:	European Research Biology Center S.r.l. Via Tito Speri, 12/14 00071 Pomezia Italy

The laboratory facilities, archives and administration are located at this site.

PROJECTED TIME PLAN

			Date
1.	Proposed experimental starting date	:	First half of February 2021
2.	Proposed experimental completion date	:	2 weeks from the start of the experimental phase
3.	QA-Audited Draft Report to Sponsor	:	2 weeks after the end of the experimental phase

Any change in the experimental design or any additional activity requested to maintain the scientific or regulatory integrity of the study might cause a change in time schedule indicated above.

1. INTRODUCTION

1.1 Objective

This test allows the identification of non-corrosive and corrosive substances and mixtures in accordance with the UN GHS (1). The test system EPISKIN™ is one of the available commercial reconstructed human *epidermis* (RhE) models used for distinguishing corrosive (C) from non-corrosive (NC) substances. It further supports the sub-categorization of corrosive substances and mixtures into optional Sub-category 1A, in accordance with the UN GHS, as well as a combination of Sub-categories 1B and 1C.

1.2 Regulatory requirements

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 50 of 2 March 2007 and subsequent revisions.

The Sponsor has affirmed that the test item is a chemical product (industrial waste) and that the study will be performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

In addition, the study is designed to comply with the experimental methods indicated in the guidelines of:

OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (Rhe) Test Method" (Adopted on 18 June 2019);

1.3 Principles of the method

The test system EPISKIN™ is a reconstructed human *epidermis* (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.,* the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue], into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item and the quality system under which the test item characterisation was performed will also be the Sponsor's responsibility.
A certificate of analysis for the test item should be supplied.

2.2 Identity

The test item will be Farmed Bauxite Residue, Q4 2019.

The following information, supplied by the Sponsor, refers to the original batch of test item received for the study:

Batch number: Q4 2019
Expiry date: not available
Storage conditions: room temperature

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used will be recorded according to standard procedures.

2.3 Preparation of test item

Test item will be used in the form supplied.
If necessary, solid substances will be ground to reduce particle size and aid suspension.

2.4 Safety precautions

The precautions necessary when handling the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under ERBC Hazard Classification System, according to ERBC standard procedures.

2.5 Disposal

Approximately 1 year after the Final Report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration or returned to the Sponsor.

3. CONTROL ITEMS

3.1 The control items are commercially obtained by ERBC. Information about the identity, strength, purity and composition or other characteristics appropriately defining these compounds, before their use in the study, as well as the stability are detailed in documents obtained from the Supplier.

3.2 Control items will be the following:
- Negative control: The preferred choice will be 0.9% (w/v) NaCl, but Distilled Water (Bieffe Medital or equivalent) can be used, if necessary.
- Positive control item: Glacial Acetic Acid.

Determination of the stability and concentration of solutions of these agents will not be undertaken since it is sufficient to provide evidence of the correct expected response of the test system to them.

4. MATERIALS AND METHODS

4.1 EPISKIN™

The test system EPISKIN™ is commercially available from SkinEthic Laboratories.

4.1.1 Characteristic of the test system

The SkinEthic reconstructed human tissue model EPISKIN™ consists of an airlifted, living, multi-layered tissue construct, produced in polycarbonate inserts in serum-free and chemically defined medium, featuring normal ultra-structure and functionality equivalent to human tissue *in vivo*.
Normal human keratinocytes are used to reconstruct the epithelium. Multiple layers of viable epithelial cells (basal layer, *stratum spinosum, stratum granulosum*) should be present under a functional *stratum corneum*. *Stratum corneum* should be multilayered containing the essential lipid profile to produce a functional barrier with robustness to resist rapid penetration of cytotoxic marker chemicals.

4.1.2 Functional conditions

The barrier function should be demonstrated. The containment properties of the RhE model should prevent the passage of material around the *stratum corneum* to the viable tissue, which would lead to poor modelling of skin exposure.
The RhE model supplier should ensure that each batch of the RhE model used meets defined production release criteria. A certificate will be supplied for each batch of the test system.

4.1.3 Preparation and storage of the test system

Within 24 hours from arrival ~~**Immediately after arrival**~~, the multiwell plate will be opened under a sterile airflow. Each insert containing the epidermal tissue will be carefully taken out. Any remaining agarose that adheres to the outer sides of the insert will be rapidly removed by gentle blotting on the sterile filter paper. Inserts will be quickly placed in a 12-well plate in which each well has previously been filled with 2 mL/well SkinEthic Maintenance Medium (pre-warmed at 37 °C) making sure that no air bubbles are formed underneath the inserts.
Culture plates will be placed in the incubator at 37°C, 5% CO_2 and saturated humidity.

Testing can initiate after at least two hours of incubation.

4.2 Media and reagents

SkinEthic Maintenance Medium Supplied with the EPISKIN™
To be stored at 2-8°C. To be used at room temperature (without pre-heating).

SkinEthic Assay Medium To be stored at 2-8°C.	Supplied with the EPISKIN™
0.9% (w/v) NaCl	
Glacial Acetic Acid	
MTT Stock Solution	3 mg/mL MTT in D-PBS.
MTT Ready-to-use Solution	MTT Stock Solution diluted 1:10 (v/v) with pre-warmed SkinEthic Assay Medium (final concentration 0.3 mg/mL of MTT).
Acidic Isopropanol	0.04 N HCl in Isopropanol
Water-killed epidermis	to be prepared only for MTT interacting reagents. Living epidermis is incubated with 2 mL of distilled water at 37°C, 5% CO_2 and saturated humidity for approximately 2 days. The water is discarded and the samples frozen at -18 to -20°C for up to 6 months.

5. EXPERIMENTAL PROCEDURE

5.1 Experimental design

Before testing the test item for corrosive properties, adequacy of the test system will be verified to ensure that the test item enters in the applicability domain of the assay.
A preliminary test will be undertaken in two steps. The test item will be checked for the ability to reduce the MTT (Step 1) and to colour water (Step 2).
The main experiment will be carried out including all controls to assess corrosive potential and classify the test item, according to the EU/GHS regulations.

5.2 Preliminary test

5.2.1 Direct MTT reduction test (Step 1)

Non-specific reduction of MTT will be evaluated as follows:
Two mL of MTT Ready-to-use Solution will be incubated with an amount of the test item (50 µL if liquid, 20 ± 2 mg if solid) and incubated at 37°C, 5% CO_2 and saturated humidity for 3 hours protected from light, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time will imply the use of water killed epidermis as a control in the main assay (additional cost).

5.2.2 Colouring potential test (Step 2)

To identify potential interference by coloured test chemicals or test chemicals that become coloured when in contact with water and decide on the need for additional controls, spectral analysis of the test chemical in water should be performed.
An amount of the test item (10 µL if liquid, 10 ± 1 mg if solid) will be added to 90 µL of distilled water in a transparent tube (vial or micro-tube). The mixture will be blended for approximately 15 minutes and spectral analysis, if necessary, will be performed at 595 nm.
Colouring of the solution (e.g. observation of blue or purple appearance) at the end of the incubation time will imply the use of alive samples treated without MTT as a control in the main assay.

5.2.3 Further preliminary test (Additional cost)

When a positive result is obtained in preliminary tests described either in section 5.2.1 or 5.2.2 (or both), further preliminary test may be conducted to quantify the ability of the test item to reduce MTT or to stain tissue before beginning the main test. The results may indicate that the test item is not suitable for the test system before beginning a complete main assay. These assays will be conducted only in agreement with the Sponsor.
Otherwise, the Main Assay will be conducted with all the appropriate controls.

5.3 Main Assay

5.3.1 Treatment scheme

A Main Assay will be carried out including the test item, positive and negative controls. A typical treatment scheme may be the following:

Basic assay:

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Negative control 1	Live tissue	0.9% NaCl or distilled water	3	2
Negative control 2	Live tissue		60 (± 5)	2
Negative control 3	Live tissue		240 (± 5)	2
Positive control	Live tissue	Glacial acetic acid	240 (± 5)	2
Test item 1	Live tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item 2	Live tissue		60 (± 5)	2
Test item 3	Live tissue		240 (± 5)	2

Additional controls

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Test item 1 *	Killed tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item 2 *			60 (± 5)	2
Test item 3 *			240 (± 5)	2
Negative control 1 *	Killed tissue	0.9% NaCl or distilled water	3	2
Negative control 2 *			60 (± 5)	2
Negative control 3 *			240 (± 5)	2
Test item without MTT 1 §	Killed tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item without MTT 2 §			60 (± 5)	2
Test item without MTT 3 §			240 (± 5)	2
Test item without MTT 1 °	Live tissue	Farmed Bauxite Residue, Q4 2019	3	2
Test item without MTT 2 °			60 (± 5)	2
Test item without MTT 3°			240 (± 5)	2

* to be added in case of test items able to reduce MTT (killed tissue will be of the same batch but the batch will be different from the alive tissue batch).
° to be added in case of test items able to stain tissue or with a potential to stain tissue.
§ to be added in case of test items able both to stain tissue and reduce MTT.

Additional experiments could be performed if necessary.

5.3.2 Treatment procedure

A sufficient amount of the test or control item (50 ± 3 µL if liquid, 20 ± 2 mg if solid, 50 ± 2 mg if waxy/sticky) will be applied to uniformely cover each epidermis surface while avoiding an infinite dose. This will allow a surface exposure of approximately 131.6 µL or mg/cm^2 (liquid or waxy/stixy substances) or 52.6 mg/cm^2 (solid substances) being the treatment area of the commercial test system equal to 0.38 cm^2. Only for solid chemicals, the epidermis surface will be moistened with 100 ± 5 µL of 0.9% NaCl solution after application of the test item. Waxy/sticky test items will be added on each single tissue with a nylon mesh, if necessary.
The exposure time will be allowed in a ventilated cabinet at room temperature. For peculiar test items (e.g. surfactant and viscous liquids), an intermediate re-spreading will be carried out, if necessary.
Each tissue will then be rinsed with approximately 25 mL of sterile PBS filling and empting the tissue insert. The excess liquid will be carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of pre-warmed maintenance medium.

5.3.3 MTT Assay

The tissue inserts and controls will be incubated with 2 mL/well of MTT ready to use solution with the exception of treated tissues without MTT which will be incubated with SkinEthic Maintenance Medium.

Plates will be incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity.
At the end of the incubation period, tissues will be placed on absorbent paper to dry. A total biopsy will be carried out by means of a specific biopsy punch supplied by SkinEthic to allow biopsies of the same dimensions. The epidermis will be separated from the collagen matrix and will both be placed in a microtube prefilled with 500 µl of acidic isopropanol. In the case of coloured collagen, unstained and untreated collagen matrices taken from killed epidermis may substitute the coloured collagen.
Tubes will be mixed by vortexing and preserved overnight at room temperature to allow formazan extraction.
At the end of the extraction period, debris will be eliminated by short centrifugation of the tubes (e.g. at 10000-14000 rpm for 2 minutes).
Aliquots of 200 µl from each sample will be read in duplicate for their absorbance at 595 nm. Optical Density (OD) values will be recorded.
On the day of the analysis, the spectrophotometer will be verified against standard solutions of MTT formazan prepared in acidic isopropanol, in order to verify if the OD values fall in the linearity range of the spectrophotometer.

5.3.4 Special procedures for control wells

Control for potentially tissue-staining test items (killed/alive epidermis)
SkinEthic Assay Medium will be added to the test item-treated well instead of MTT solution. All other procedures will be carried out as described for the main assay.

Water killed epidermis control
Before use, tissues will be thawed by incubation at room temperature with 2 mL of SkinEthic Maintenance Medium for at least one hour. All other procedures will be carried out as described for the Main Assay.

6. EVALUATION OF RESULTS

6.1 Study acceptability criteria

Blank controls: mean OD value < 0.1
Negative controls (for each exposure time point): mean OD value ≥ 0.6 and ≤ 1.5
Positive controls: mean viability expressed as percentage of the negative control ≤ 20%
Intra-replicate variability: in the range 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

6.2 Interpretation of results and classification as corrosive

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, relative and mean relative viability values (percentage relative to the negative control) will be calculated.

Cut-off values for the endpoint of the test are established as follows:

Viability related to concurrent negative control	Classification
< 35% after 3 min exposure	**Corrosive:** • Sub-categoria 1A (optional)
≥ 35% after 3 min exposure **AND** < 35% after 60 min exposure **OR** ≥ 35% after 60 min exposure **AND** < 35% after 240 min exposure	**Corrosive:** • A combination of sub-categories 1B and 1C (optional)
≥ 35% after 240 min exposure	**Non-corrosive**

For direct MTT interacting test items, non specific MTT reduction calculation (NSMTT) relative to the Negative Control will be evaluated as follows:

$$NSMTT = 100 \times \frac{OD_{\text{treated killed tissues}} - OD_{\text{non-treated killed tissues}}}{OD_{\text{negative control living tissues}}}$$

The NSMTT control per exposure time will be performed concurrently to the testing of the coloured test item.
If the NSMTT ≤ 5% only blank subtraction will be carried out.
If 5% < NSMTT ≤ 50% blank and appropriate background subtraction will be carried out.
If NSMTT > 50% results should be taken with caution.

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control will be evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{\text{test item (not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

The NSC_{living} control per exposure time will be performed concurrently to the testing of the coloured test item and in case of multiple testing, an independent NSC control will be conducted with each test performed (in each run).
If the $NSC_{living} \leq 5\%$ only blank subtraction will be carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction will be carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

For test items able both to stain tissue and reduce MTT, to avoid a possible double correction for colour interference, a third control for Non Specific Colour in killed tissues (NSC_{killed}) will be evaluated per exposure time:

$$NSC_{killed} = 100 \times \frac{OD_{\text{test item (treated killed tissues not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

If the $[(NSMTT + NSC_{living}) - NSC_{killed}] \leq 5\%$ this value will not be considered for the final calculation.

If 5% < [(NSMTT + NSC_{living}) - NSC_{killed}] ≤ 50% blank subtraction and appropriate background subtraction will be carried out.
If [(NSMTT + NSC_{living}) - NSC_{killed}] > 50% results should be taken with caution.

A single NSC_{killed} control is sufficient per test item regardless of the number of independent tests/runs performed, but should be performed concurrently to the NSMTT control.

The above corrections should be applied when the mean OD value of test item treated tissues without any correction is within the linearity range of the spectrophotometer. In case of strong interference (OD values out of the linear range) the test item is not suitable for this test method.

7. REPORTING

7.1 Presentation of data

The results will be presented in the form of tables.

7.2 Interim Report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.3 Final Report

A Draft Report will be sent to the Sponsor together with the Draft Report Approval Form. With the exception of signatures, the Draft Report will contain all information and data included in the Final Report.
Comments made by the Sponsor may be incorporated and the Final Report will be issued. If comments are not received within 6 months from despatch of the Draft Report, the Final Report will be issued.
The Final Report will include the information and data required by current internationally recognised regulations. The Final Report, digitally signed or with handwritten signatures, will be issued as PDF file, searchable, bookmarked and hyperlinked, fully compliant with the standard PDF/A-1b (ISO 19005-1 Level B), suitable for long term archiving of electronic document.

7.4 Corrections or additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the Final Report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations. Prior to final archiving of the study data, a full list will be prepared of all records associated with the study.
A reserve sample of each batch of the test item will be taken and kept under the storage conditions of the bulk supply at ERBC. The reserve sample(s) of the test item will be retained within ERBC archives for a period of 10 years and then destroyed.

Any biological samples obtained for analytical measurements or similar determinations will be managed as indicated by the Sponsor in the Draft Report Approval Form or otherwise destroyed at no charge within 3 months from the issue of the Final Report.

The Final Protocol, the Final Report and electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower, where used) will be archived at ERBC.

All other specimens, raw data, records and documentation generated during the course of this study will be archived at ERBC for a period of 3 years, after which the Sponsor will be contacted for shipment or disposal of the material (expenses will be charged to the Sponsor).

9. STUDY CONDUCT

9.1 Language

English and Italian renderings of chemical names, including that of the test material will be considered to be equivalent.

9.2 Scientific decisions

The procedures described in this Protocol may not comprehensively cover all the circumstances that can arise in the assay of the test items. When the study director considers it advisable to modify the procedures described for the selection of a solvent, interpretation of the outcome of the study or other aspects of the study conduct, he/she will carefully record the decision he/she has reached and the reasoning which led to it.

9.3 Quality assurance

According to the ERBC quality assurance programme, defined in the ERBC QA SOPs, this study will be subjected to the following procedures:

- the Protocol will be inspected,
- study/process based inspections of procedures/facilities will be carried out at intervals adequate to assure the integrity of the study,
- the Report will be inspected to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to Management and Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's Representative and Regulatory Authorities.

10. RESPONSIBILITIES OF THE SPONSOR

Items which are the responsibility of the Sponsor are indicated in section 2 of this Protocol. Since full compliance with regulatory requirements may depend on the performance of these items, the Sponsor should ensure that appropriate actions are initiated or undertaken.

11. REFERENCES

United Nations (UN) (2005). Globally Harmonised System of Classification and Labelling of Chemicals (GHS), First revised edition, UN New York and Geneva 2005.

ECVAM Protocol for EPISKIN™: an In Vitro Assay for Assessing Dermal Corrosivity Standard Operating Procedure (October 2000).

ICCVAM Evaluation of EPISKIN™, EpiDerm™ (EPI-200), and the Rat Skin Transcutaneous Electrical Resistance (TER) Assay: In Vitro test methods for Assessing Dermal Corrosivity Potential of Chemicals (NIH Publication No: 02-4502).

INVITTOX Protocol No. 118 EPISKIN™ Skin Corrosivity Test.

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

ERBC S.r.l.

VERIFIED BY : _____ 17-Mar-2021
S. Cinelli, Biol.D., ERT — Date
Associate Scientific Director,
Head of Genetic Toxicology & Alternative Methods

APPROVED BY : _____ 17 Mar 2021
L. Bisini, Biol.D. — Date
Study Director

Version 20/1

PROTOCOL AMENDMENT 1

APPROVAL PAGE

for

Aughinish Alumina Ltd.

AUTHORISED BY : _____ 18/03/2021.
Date

Name and Title : R. O'Dwyer
Senior Environmental Engeneer

THE
NON-CLINICAL
ENGINE

EUROPEAN RESEARCH BIOLOGY CENTER

Farmed Bauxite Residue, Q3 2020

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL

(EPISKIN™/MTT method)

FINAL REPORT

ERBC STUDY NO. A4370

Sponsor:
Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

COMPLIANCE STATEMENT

I, the undersigned, was responsible for the preparation of this report and hereby declare that it constitutes a true and faithful account of the procedures adopted and of the results obtained in the performance of the study. The aspects of the study conducted by European Research Biology Center S.r.l. were performed in accordance with:

1. Decreto Legislativo 2/3/2007 n. 50, Attuazione delle direttive 2004/9/CE e 2004/10/CE, concernenti l'ispezione e la verifica della Buona Pratica di Laboratorio (BPL) ed il ravvicinamento delle disposizioni legislative, regolamentari ed amministrative relative all'applicazione dei principi di Buona Pratica di Laboratorio ed al controllo della loro applicazione per le prove sulle sostanze chimiche (G.U. 13/4/2007, Serie generale n. 86) and subsequent revisions.
2. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004, on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances.
3. ENV/MC/CHEM(98)17 OECD principles on Good Laboratory Practice (as revised in 1997).

DIGITAL SIGNATURE

L. Bisini, Biol.D.
STUDY DIRECTOR

Date

KEY STUDY STAFF

L. Bisini	Study Director - Head of Genetic Toxicology & Alternative Methods Department from 1st October 2021
R. Zanier	Head of Quality Assurance
S. Cinelli	Associate Scientific Director, Head of Genetic Toxicology & Alternative Methods until 30th September 2021

Test Facility Management

S. Venturella, Biol.D., ERT	Test Facility Director

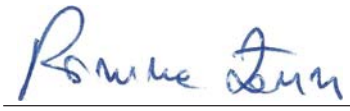
QUALITY ASSURANCE STATEMENT

Study phases	Inspection dates	Report to SD[a]	Report to CM[b]
Study Plan			
Study Plan check	01.07.2021	01.07.2021	01.07.2021
Process based inspections related to this type of study			
Dose preparation	24.08.2021	-	24.08.2021
Test execution	07.07.2021	-	08.07.2021
Final Report (end of review)	*date of QA Statement signature*		

[a] *SD = Study Director only for protocol check and study based inspections*
[b] *CM = Company Management*

Other QA process based inspections were carried out on departments or laboratories performing routine activities (e.g. Analytical Chemistry, Histopathology, Veterinary Services and Clinical Pathology) as well as on other routine activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here. Involved departments or laboratories and support functions are also subject to regular facility inspections.

Review of this report by ERBC QA found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.



12th October 2021

R. Zanier, CMB, Ph.D.
HEAD OF QA

Date

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1 SUMMARY

The potential of the test item Farmed Bauxite Residue, Q3 2020 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™. The experimental procedures are based on the OECD Guideline for testing of chemicals no. 431. The test item, as well as controls, were tested for their ability to impair cell viability after an exposure period of 3, 60 and 240 minutes. The final endpoint of the assay is the colorimetric measurement of MTT reduction (blue formazan salt) in the test system, being this reaction an index of cell viability. The test item was tested as supplied by the Sponsor.

A preliminary test was carried out to evaluate the compatibility of the test item with the test system. In a first step, the test item was assayed for the ability of reducing MTT *per se*. A brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Therefore, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

In the Main Assay, for each treatment time, the test item (physical state: solid) was applied as supplied in two replicates, at the treatment level of 20±2 mg/*epidermis* unit, each measuring 0.38 cm^2 (treatment level: 52.6 mg/cm^2). Positive and negative controls (Glacial acetic acid and Physiological saline, respectively) were concurrently tested, in the same number of replicates and test conditions at the treatment level of 50 µL/*epidermis* unit. Positive control was included only at the longest treatment time of 240 minutes, while a negative control was included for each treatment time.

In the Main Assay, the negative controls gave the expected baseline value (Optical Density values ≥ 0.6 and ≤ 1.5) and variability (difference of viability between the two replicates lower than 30%), at each treatment time, in agreement with the guideline indications. For each treatment time, the concurrent negative control mean value is considered the baseline value of the treatment series and thus represents 100% of cell viability.

The positive control caused the expected cell death (0.8 % of cell viability, when compared to the negative control).

Based on the stated criteria, the assay was regarded as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

The test item did not induce cell death in any replicate, at any treatment time. Each mean cell viability, after the concurrent blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	106
60	112
240	115

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q3 2020 is identified as non-corrosive to the skin.

2 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the potential skin corrosion of the test item as measured by its ability to induce cell death in a commercial reconstructed human epidermis (RhE) model, EPISKIN™.

2.2 Regulatory compliance

Experimental procedures were based on the following guideline:

- OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method" (Adopted on 18 June 2019).

The Sponsor affirmed that the test item is a chemical product (industrial waste) and that the study was performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

2.3 Principle of the test

The test system EPISKIN™ is a reconstructed human epidermis (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.*, the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue; CAS N. 298-93-1] into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2.4 Sponsor and Test Facility

The study was performed at:

European Research Biology Center S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

On behalf of the Sponsor:

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

2.5 Study schedule

Procedure	**Date**
Protocol approved by: Study Director	 30 June 2021
Start of experimental phase Preliminary test	 01 July 2021
End of experimental phase Completion of scoring of Main Assay	 29 July 2021
Study completion	Date of Study Director's signature on this report

3 TEST ITEM AND CONTROL ITEMS

3.1 Test Item

3.1.1 Identity

Details of the test item received at ERBC were as follows:

Identity	Farmed Bauxite Residue, Q3 2020
Label name	Q3 2020 SAMPLE2
Alternative name	Bauxite Residue
Batch no.	Q3 2020
Expiry date	03 June 2022
Storage conditions	Room temperature
ERBC no.	17438

The determination of the identity, strength, purity, composition and stability as well as the quality system used in the test item characterisation were responsibility of the Sponsor

. The certificate of analysis is presented in Addendum 1 of this report. A sample of test item was taken and will be stored in the archives of ERBC for 10 years prior to disposal.

3.2 Control Items

Positive control item was Glacial acetic acid (C. Erba, batch no. P6NO24277B).

Negative control item was Physiological saline (Baxter, batch no. 19H0603).

Positive and negative control items were obtained commercially and characterised by labelling. Determination of the stability and concentration of solutions of positive and negative controls were not undertaken, since it is sufficient to provide evidence for the correct expected response of the test system to them.

4 METHODS

4.1 Test System

4.1.1 EPISKIN™

Commercial Name	EPISKIN™ Small/Human Epidermis (SM/13) - (0.38 cm^2)
Supplier	SkinEthic Laboratories (4, A. Fleming – 69366 Lyon – France)
Batch	21-EKIN-030
Arrived at ERBC on	27 July 2021

Functional controls

Quality controls: histology scoring, magnitude of viability and barrier function (IC_{50} determination).

Biological safety: absence of HIV1 and 2 antibodies, hepatitis C antibodies, hepatitis B antigen HBs, absence of bacteria, fungi and mycoplasma.

A certificate of analysis can be found in Addendum 2.

4.1.2 Preparation of the Test System

Examination at arrival

pH indicator: orange (suitable for use)

Preparation and pre-treatment incubation period

According to the supplier procedure, at arrival, plates were opened under a sterile airflow and each insert, containing the epidermal tissue, was carefully taken out and placed in a 12-well plate in which each well had previously been filled with 2 mL/well SkinEthic Maintenance Medium. Culture plates were placed in the incubator at 37°C, 5% CO_2 and saturated humidity for approximately 24 hours.

4.2 Media

Maintenance Medium	SkinEthic; batch: 21-MAIN3-029
Assay Medium	SkinEthic; batches: 21 ESSC 025 and 21 ESSC 028

4.3 Experimental procedure

4.3.1 Preliminary test

Direct MTT reduction test (Step 1)

Non-specific reduction of MTT was evaluated as follows: two mL of MTT ready-to-use solution (0.3 mg/mL) was incubated with 20±2 mg of test item at 37°C, 5% CO_2 and saturated

humidity for 3 hours, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time was carried out.

Colouring potential test (Step 2)

Chemicals' colouring potential was assessed for potential interaction with the test system. 10±1 mg of test item was added to 90 µL of distilled water (Galenica senese; batch no. 2100209) in a transparent tube and the resulting solution/suspension mixed by using a vortex for 15 minutes. Colouring of the suspension at the end of the incubation time was evaluated by unaided eye.

4.3.2 Main Assay

Treatment

In Main Assay, alive tissues were treated with the test item, positive and negative controls. The treatment scheme was the following:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Negative control	Live tissue	Physiological saline	3	50 µL	2	CN1A, CN1B
Negative control	Live tissue	Physiological saline	60	50 µL	2	CN2A, CN2B
Negative control	Live tissue	Physiological saline	240	50 µL	2	CN3A, CN3B
Positive control	Live tissue	Glacial acetic acid	240	50 µL	2	CP1A, CP1B
Test item	Live tissue	Farmed Bauxite Residue, Q3 2020	3	20±2 mg	2	TI-B1A, TI-B1B
Test item	Live tissue	Farmed Bauxite Residue, Q3 2020	60	20±2 mg	2	TI-B2A, TI-B2B
Test item	Live tissue	Farmed Bauxite Residue, Q3 2020	240	20±2 mg	2	TI-B3A, TI-B3B

Additional controls were included in the Main Assay with the following treatment scheme:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q3 2020	3	20±2 mg	2	CC-B1A, CC-B1B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q3 2020	60	20±2 mg	2	CC-B2A, CC-B2B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q3 2020	240	20±2 mg	2	CC-B3A, CC-B3B

After application of the test item, the epidermis surfaces were moistened with 100±5 µL of 0.9% NaCl solution.

Exposure period

Exposure times of 3, 60±5 and 240±5 minutes were allowed in a ventilated cabinet at room temperature.

Washing

At the end of the exposure, each tissue was rinsed with approximately 25 mL of sterile PBS, filling and empting the tissue insert. The excess liquid was carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of maintenance medium.

MTT staining

Each tissue insert was incubated with 2 mL/well of MTT ready-to-use solution. Plates were incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity. At the end of the incubation period, tissues were placed on absorbent paper to dry. A total biopsy was carried out by means of a biopsy punch to allow biopsies of the same dimensions.

The epidermis were separated from the collagen matrix and both placed in a microtube prefilled with 500 µL of acidic isopropanol. Tubes were mixed by vortexing and preserved overnight at room temperature to allow formazan extraction. At the end of the extraction period, debris were eliminated by short centrifugation of the tubes (14000 rpm for 2 minutes) and aliquots of 200 µL from each sample were read in duplicate for their absorbance at 595 nm. Six aliquots (200 µL) of acidic isopropanol were analysed and used as blank. An MTT formazan calibration curve was performed in order to ensure that OD values obtained in the main experiment were within the spectrophotometer linear range.

4.4 Analysis and evaluation of data

4.4.1 Study Acceptability Criteria

The assay was considered valid if the following criteria were met:

- Blank controls: mean OD value < 0.1.

- Negative controls: mean OD value ≥ 0.6 and ≤ 1.5, difference of viability between the two replicates ≤ 30%.
- Positive controls: mean viability expressed as percentage of the negative control ≤ 20%.
- In the range of 20-100% viability and for ODs ≥ 0.3, difference of viability between the two replicate cultures treated with the test item ≤ 30%.

4.4.2 Interpretation of results and classification

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, mean relative viability values (percentage relative to the concurrent negative control) were calculated.

Cut-off values for the endpoint of the test are established as follows:

Criteria	Classification
< 35% after 3 min exposure	Corrosive Sub-categoria 1A
≥ 35% after 3 min exposure AND < 35% after 60 min exposure OR ≥ 35% after 60 min exposure AND < 35% after 240 min exposure	Corrosive: combination of sub-categories 1B and 1C
≥ 35% after 240 min exposure	Non- Corrosive

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control is evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{test\ item(not\ incubated\ with\ MTT)}}{OD_{negative\ control\ living\ tissues}}$$

If the $NSC_{living} \leq 5\%$ only blank subtraction is carried out.

If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction is carried out.

If $NSC_{living} > 50\%$ the test item is not suitable for this test method.

4.5 Protocol deviations

No deviation occurred during the study.

4.6 Archives

Full records of all aspects of the study conduct were maintained together with the results of all measurements and observations. All specimens, raw data, records and documentation

generated during the course of this study will be retained within ERBC archives. The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. The Final Protocol, the Final Report and, where applicable, electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower), will be archived at ERBC.

5 RESULTS

5.1 Preliminary test

Before the Main Assay, a preliminary test was carried out to evaluate the compatibility of the test item with the test system. Results of this preliminary test can be found in Table 1.

In a first step, the test item was assayed for the ability of reducing MTT *per se*. A brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. Thus no additional controls were added in the main phase for the evaluation of MTT non-specific reduction. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Thus, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

5.2 Main Assay

A Main Assay was performed. Raw data and data elaboration are reported in Table 2.

The mean Optical Density of Blank Controls was 0.038, lower than the maximum acceptable value (0.1). All negative control mean OD values gave the expected baseline value and variability, in agreement with guideline indications. According to the method, each negative control mean value is considered the baseline value for the concurrent treatment series, thus they represent 100% of cell viability.

Positive control results indicated an appropriate cell death with an acceptable relative cell viability (0.8% of the negative control value).

Based on the stated criteria, the study was accepted as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

The test item did not induce cell death in any replicate, at any treatment time. Each mean cell viability, after the blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	106
60	112
240	115

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q3 2020 is identified as non-corrosive to the skin.

6 CONCLUSION

The potential of the test item Farmed Bauxite Residue, Q3 2020 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.

The blank, negative and positive controls gave acceptable results at all treatment times, thus the study was accepted as valid.

The mean cell viability of the test item treated tissues, after the blank subtraction, was higher than 35% at all treatment times. Based on the results obtained, the test item Farmed Bauxite Residue, Q3 2020 is identified as non-corrosive to the skin.

7 TABLES

Farmed Bauxite Residue, Q3 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN^{TM}/MTT method)

STUDY NO.: A4370

PRELIMINARY TEST

Direct MTT reduction test (Step 1)

Test item (mg)	**MTT ready to use solution (mL)**	**Container**	**Incubation condition**	**Colour Observation**
20 ± 2	2.0	well	3 h at 37°C, 100% nominal humidity 5% CO_2	Brown suspension, with brown precipitate (no interaction)

Colouring potential test (Step 2)

Test item (mg)	**Water (µL)**	**Container**	**Incubation condition**	**Colour Observation**
10 ± 1	90	Eppendorf tube	15', ambient condition, in agitation	Brown suspension (possible interaction)

Farmed Bauxite Residue, Q3 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4370

MAIN ASSAY

TREATMENT TIME: 3 minutes

BLANK		**Negative Control**						
	OD_{blank}					**OD_{NC}**		**Viability (%)**
	0.0364	CN1A-1	0.7168	0.6792		0.6936		94.7
	0.0394	CN1A-2	0.7456	0.7080				
	0.0364	CN1B-1	0.7957	0.7581		0.7705		105.3
	0.0362	CN1B-2	0.8205	0.7829				
	0.0366							
	0.0405							
Mean	0.038	**Mean**		0.732	**Mean**	0.732		100
SD	0.0019	**SD**		0.047				
CV(%)	4.98	**CV(%)**		6.4			**Δ (%)**	10.5
		Test Item						
						OD_{TI}		**Viability (%)**
		TI-B1A-1	0.7474	0.7098		0.7106		97.1
		TI-B1A-2	0.7489	0.7113				
		TI-B1B-1	0.9161	0.8785		0.8428		115.1
		TI-B1B-2	0.8446	0.8070				
		Mean		0.777	**Mean**	0.777		**106**
		SD		0.082				
		CV(%)		10.5			**Δ (%)**	17.0
		Test Item without MTT						
						ODcc		**NSCliving (%)**
		CC-B1A-1	0.0463	0.0087		0.0088		1.2
		CC-B1A-2	0.0465	0.0089				
		CC-B1B-1	0.0407	0.0031		0.0092		1.3
		CC-B1B-2	0.0529	0.0153				
		Mean		0.009	**Mean**	0.009		**1**
		SD		0.005				
		CV(%)		55.3			**Δ (%)**	4.4

Farmed Bauxite Residue, Q3 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4370

MAIN ASSAY

TREATMENT TIME: 60 minutes

BLANK		**Negative Control**						
	OD_{blank}					**OD_{NC}**		**Viability (%)**
	0.0364	CN2A-1	0.7946	0.7570		0.7834		92.8
	0.0394	CN2A-2	0.8474	0.8098				
	0.0364	CN2B-1	0.9216	0.8840		0.9046		107.2
	0.0362	CN2B-2	0.9627	0.9251				
	0.0366							
	0.0405							
Mean	0.038	**Mean**		0.844	**Mean**	0.844		100
SD	0.0019	**SD**		0.075				
CV(%)	4.98	**CV(%)**		8.9			**Δ (%)**	14.4
		Test Item						
						OD_{TI}		**Viability (%)**
		TI-B2A-1	0.9521	0.9145		0.9362		110.9
		TI-B2A-2	0.9954	0.9578				
		TI-B2B-1	0.9797	0.9421		0.9529		112.9
		TI-B2B-2	1.0013	0.9637				
		Mean		0.945	**Mean**	0.945		**112**
		SD		0.022				
		CV(%)		2.3			**Δ (%)**	1.8
		Test Item without MTT						
						ODcc		**NSCliving (%)**
		CC-B2A-1	0.0666	0.0290		0.0165		2.0
		CC-B2A-2	0.0415	0.0039				
		CC-B2B-1	0.0457	0.0081		0.0068		0.8
		CC-B2B-2	0.0431	0.0055				
		Mean		0.012	**Mean**	0.012		**1**
		SD		0.012				
		CV(%)		100.6			**Δ (%)**	82.9

Farmed Bauxite Residue, Q3 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4370

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**						
	OD_{blank}					**OD_{NC}**		**Viability (%)**
	0.0364	CN3A-1	0.7485	0.7109		0.7324		92.7
	0.0394	CN3A-2	0.7915	0.7539				
	0.0364	CN3B-1	0.8758	0.8382		0.8481		107.3
	0.0362	CN3B-2	0.8956	0.8580				
	0.0366							
	0.0405							
Mean	0.038	**Mean**		0.790	**Mean**	0.790		100
SD	0.0019	**SD**		0.070				
CV(%)	4.98	**CV(%)**		8.8			**Δ (%)**	14.6
		Test Item						
						OD_{TI}		**Viability (%)**
		TI-B3A-1	0.9069	0.8693		0.8775		111.0
		TI-B3A-2	0.9232	0.8856				
		TI-B3B-1	0.9771	0.9395		0.9466		119.8
		TI-B3B-2	0.9913	0.9537				
		Mean		0.912	**Mean**	0.912		**115**
		SD		0.041				
		CV(%)		4.5			**Δ (%)**	7.6
		Test Item without MTT						
						ODcc		**NSCliving (%)**
		CC-B3A-1	0.0388	0.0012		0.0055		0.7
		CC-B3A-2	0.0474	0.0098				
		CC-B3B-1	0.0383	0.0007		0.0011		0.1
		CC-B3B-2	0.039	0.0014				
		Mean		0.003	**Mean**	0.003		**0**
		SD		0.004				
		CV(%)		132.5			**Δ (%)**	135.2

Farmed Bauxite Residue, Q3 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4370

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0364	CN3A-1	0.7485	0.7109		0.7324	92.7
	0.0394	CN3A-2	0.7915	0.7539			
	0.0364	CN3B-1	0.8758	0.8382		0.8481	107.3
	0.0362	CN3B-2	0.8956	0.8580			
	0.0366						
	0.0405						
Mean	0.038	**Mean**		0.790	**Mean**	0.790	100.0
SD	0.0019	**SD**		0.070			
CV(%)	4.98	**CV(%)**		8.8		**Δ (%)**	14.6

Positive control					
				OD_{TI}	**Viability (%)**
CP1A-1	0.0493	0.0117		0.0083	1.0
CP1A-2	0.0424	0.0048			
CP1B-1	0.0421	0.0045		0.0040	0.5
CP1B-2	0.0410	0.0034			
Mean		0.006	**Mean**	0.006	**0.8**
SD		0.004			
CV(%)		61.8		**Δ (%)**	70.30

8 ADDENDA

RUSAL
AUGHINISH

Aughinish Alumina Ltd.
Aughinish Island
Askeaton

Co. Limerick

IRELAND

CERTIFICATE OF ANALYSIS

Sample Type	:	Farmed bauxite residue
Sample mass	:	10g (approx.) per sample
Report Issued	:	18/06/2021

Sample	% Moisture	Units	Method
Farmed Bauxite Residue, Q2 2020	22.5	%w/w	ATM047
Farmed Bauxite Residue, Q3 2020	24.5	%w/w	ATM047

Jason Clohessy

LABORATORY QUALITY MANAGER
Jason Clohessy

"This report relates only to the items tested and shall not be reproduced except in full and with the approval of the Laboratory of Aughinish Alumina Ltd".

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS

CCE-091-SM D13-S/04

NAME

EpiSkin™ Small / Human Epidermis (SM/13)

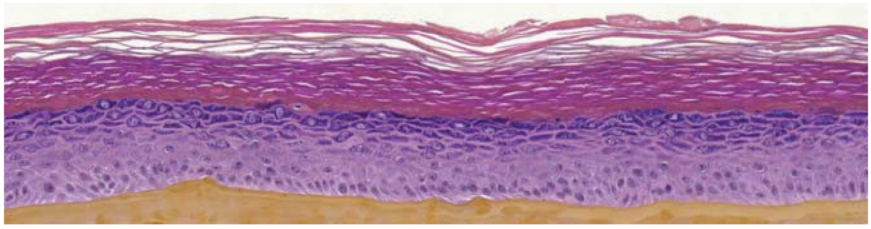
DESCRIPTION

0.38 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on a collagen matrix, for 13 days

BATCH : **21-EKIN-030**
ORIGIN : Adult donors
USAGE : FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN
STORAGE : This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO2 with saturated humidity

QUALITY CONTROLS

Control # E210978

	Process	Specification	Result
HISTOLOGY	HES stained paraffin section	Multi-layered, highly differentiated epidermis consisting of organized basal, spinous and granular layers, and a multilayered *stratum corneum*	**Satisfactory**
		Number of cell layers ≥ 4	**7.5 cell layers**
			
IC50 DETERMINATION	SDS concentration, MTT test.	1.5 mg/mL ≤ IC50 ≤ 3.0 mg/mL	**1.8 mg/mL**

BIOLOGICAL SAFETY:

On blood of the donors, we have verified the absence of HIV1 and 2 antibodies, hepatitis C antibodies and hepatitis B antigen HBs.
On cells from the donors, we have verified the absence of bacteria, fungus and mycoplasma.

SUGGESTED EXPIRATION DATE:

August 2, 2021

Lyon, July 27, 2021
Certified and released by Michel BATAILLON, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

The use of this human tissue is strictly limited to *in vitro* testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited.

ISO 9001 Certified
4, rue Alexander Fleming - 69366 Lyon Cedex 07 - France - Tél : +33 (0)4 37 28 72 00 - Fax : +33 (0)4 37 28 72 28
S.A. au capital de 13 608 807 € - 412 127 565 R.C.S. Lyon - NAF : 7211 Z - N° TVA Intracommunautaire FR 46 412 127 565
www.episkin.com

THE
NON-CLINICAL
ENGINE
EUROPEAN RESEARCH BIOLOGY CENTER

Version 20/2

Farmed Bauxite Residue, Q3 2020
***IN VITRO* SKIN CORROSION STUDY USING A**
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

Final Protocol
prepared for

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

by

EUROPEAN RESEARCH BIOLOGY CENTER S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

ERBC Study Number: A4370
ERBC Enquiry Number: O2631

June 2021

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www.erbc-group.com

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

MANAGEMENT OF STUDY

Study Director	:	L. Bisini, Biol.D. lbisini@erbc-group.com
Sponsor	:	Aughinish Alumina Ltd. Aughinish island, Askeaton Co. Limerick Ireland
Monitor	:	R. O'Dwyer

QUALITY ASSURANCE

Head of QA	:	R. Zanier, CMB, Ph.D.

LOCATION OF STUDY

The study will be performed at	:	European Research Biology Center S.r.l. Via Tito Speri, 12/14 00071 Pomezia Italy

The laboratory facilities, archives and administration are located at this site.

PROJECTED TIME PLAN

			Date
1.	Proposed experimental starting date	:	First half of July 2021
2.	Proposed experimental completion date	:	6 weeks from the start of the experimental phase
3.	QA-Audited Draft Report to Sponsor	:	4 weeks after the end of the experimental phase

Any change in the experimental design or any additional activity requested to maintain the scientific or regulatory integrity of the study might cause a change in time schedule indicated above.

1. INTRODUCTION

1.1 Objective

This test allows the identification of non-corrosive and corrosive substances and mixtures in accordance with the UN GHS (1). The test system EPISKIN™ is one of the available commercial reconstructed human *epidermis* (RhE) models used for distinguishing corrosive (C) from non-corrosive (NC) substances. It further supports the sub-categorization of corrosive substances and mixtures into optional Sub-category 1A, in accordance with the UN GHS, as well as a combination of Sub-categories 1B and 1C.

1.2 Regulatory requirements

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 50 of 2 March 2007 and subsequent revisions.

The Sponsor has affirmed that the test item is a chemical product (industrial waste) and that the study will be performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

In addition, the study is designed to comply with the experimental methods indicated in the guidelines of:

OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (Rhe) Test Method" (Adopted on 18 June 2019);

1.3 Principles of the method

The test system EPISKIN™ is a reconstructed human *epidermis* (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.,* the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue], into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item and the quality system under which the test item characterisation was performed will also be the Sponsor's responsibility.
A certificate of analysis for the test item should be supplied.

2.2 Identity

The test item will be Farmed Bauxite Residue, Q3 2020.

The following information, supplied by the Sponsor, refers to the original batch of test item received for the study:

Alternative name: Bauxite residue
Batch number: Q3 2020
Expiry date: not available
Storage conditions: room temperature

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used will be recorded according to standard procedures.

2.3 Preparation of test item

Test item will be used in the form supplied.
If necessary, solid substances will be ground to reduce particle size and aid suspension.

2.4 Safety precautions

The precautions necessary when handling the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under ERBC Hazard Classification System, according to ERBC standard procedures.

2.5 Disposal

Approximately 1 year after the Final Report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration or returned to the Sponsor.

3. CONTROL ITEMS

3.1 The control items are commercially obtained by ERBC. Information about the identity, strength, purity and composition or other characteristics appropriately defining these compounds, before their use in the study, as well as the stability are detailed in documents obtained from the Supplier.

3.2 Control items will be the following:
- Negative control: The preferred choice will be 0.9% (w/v) NaCl, but Distilled Water (Bieffe Medital or equivalent) can be used, if necessary.
- Positive control item: Glacial Acetic Acid.

Determination of the stability and concentration of solutions of these agents will not be undertaken since it is sufficient to provide evidence of the correct expected response of the test system to them.

4. MATERIALS AND METHODS

4.1 EPISKIN™

The test system EPISKIN™ is commercially available from SkinEthic Laboratories.

4.1.1 Characteristic of the test system

The SkinEthic reconstructed human tissue model EPISKIN™ consists of an airlifted, living, multi-layered tissue construct, produced in polycarbonate inserts in serum-free and chemically defined medium, featuring normal ultra-structure and functionality equivalent to human tissue *in vivo*.
Normal human keratinocytes are used to reconstruct the epithelium. Multiple layers of viable epithelial cells (basal layer, *stratum spinosum, stratum granulosum*) should be present under a functional *stratum corneum*. *Stratum corneum* should be multilayered containing the essential lipid profile to produce a functional barrier with robustness to resist rapid penetration of cytotoxic marker chemicals.

4.1.2 Functional conditions

The barrier function should be demonstrated. The containment properties of the RhE model should prevent the passage of material around the *stratum corneum* to the viable tissue, which would lead to poor modelling of skin exposure.
The RhE model supplier should ensure that each batch of the RhE model used meets defined production release criteria. A certificate will be supplied for each batch of the test system.

4.1.3 Preparation and storage of the test system

Immediately after arrival, the multiwell plate will be opened under a sterile airflow. Each insert containing the epidermal tissue will be carefully taken out. Any remaining agarose that adheres to the outer sides of the insert will be rapidly removed by gentle blotting on the sterile filter paper. Inserts will be quickly placed in a 12-well plate in which each well has previously been filled with 2 mL/well SkinEthic Maintenance Medium (pre-warmed at 37 °C) making sure that no air bubbles are formed underneath the inserts.

Culture plates will be placed in the incubator at 37°C, 5% CO_2 and saturated humidity.
Testing can initiate after at least two hours of incubation.

4.2 Media and reagents

SkinEthic Maintenance Medium Supplied with the EPISKIN™
To be stored at 2-8°C. To be used at room temperature (without pre-heating).

SkinEthic Assay Medium To be stored at 2-8°C.	Supplied with the EPISKIN™
0.9% (w/v) NaCl	
Glacial Acetic Acid	
MTT Stock Solution	3 mg/mL MTT in D-PBS.
MTT Ready-to-use Solution	MTT Stock Solution diluted 1:10 (v/v) with pre-warmed SkinEthic Assay Medium (final concentration 0.3 mg/mL of MTT).
Acidic Isopropanol	0.04 N HCl in Isopropanol
Water-killed epidermis	to be prepared only for MTT interacting reagents. Living epidermis is incubated with 2 mL of distilled water at 37°C, 5% CO_2 and saturated humidity for approximately 2 days. The water is discarded and the samples frozen at -18 to -20°C for up to 6 months.

5. EXPERIMENTAL PROCEDURE

5.1 Experimental design

Before testing the test item for corrosive properties, adequacy of the test system will be verified to ensure that the test item enters in the applicability domain of the assay.
A preliminary test will be undertaken in two steps. The test item will be checked for the ability to reduce the MTT (Step 1) and to colour water (Step 2).
The main experiment will be carried out including all controls to assess corrosive potential and classify the test item, according to the EU/GHS regulations.

5.2 Preliminary test

5.2.1 Direct MTT reduction test (Step 1)

Non-specific reduction of MTT will be evaluated as follows:
Two mL of MTT Ready-to-use Solution will be incubated with an amount of the test item (50 µL if liquid, 20 ± 2 mg if solid) and incubated at 37°C, 5% CO_2 and saturated humidity for 3 hours protected from light, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time will imply the use of water killed epidermis as a control in the main assay (additional cost).

5.2.2 Colouring potential test (Step 2)

To identify potential interference by coloured test chemicals or test chemicals that become coloured when in contact with water and decide on the need for additional controls, spectral analysis of the test chemical in water should be performed.
An amount of the test item (10 µL if liquid, 10 ± 1 mg if solid) will be added to 90 µL of distilled water in a transparent tube (vial or micro-tube). The mixture will be blended for approximately 15 minutes and spectral analysis, if necessary, will be performed at 595 nm.
Colouring of the solution (e.g. observation of blue or purple appearance) at the end of the incubation time will imply the use of alive samples treated without MTT as a control in the main assay.

5.2.3 Further preliminary test (Additional cost)

When a positive result is obtained in preliminary tests described either in section 5.2.1 or 5.2.2 (or both), further preliminary test may be conducted to quantify the ability of the test item to reduce MTT or to stain tissue before beginning the main test. The results may indicate that the test item is not suitable for the test system before beginning a complete main assay. These assays will be conducted only in agreement with the Sponsor.
Otherwise, the Main Assay will be conducted with all the appropriate controls.

5.3 Main Assay

5.3.1 Treatment scheme

A Main Assay will be carried out including the test item, positive and negative controls. A typical treatment scheme may be the following:

Basic assay:

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Negative control 1	Live tissue	0.9% NaCl or distilled water	3	2
Negative control 2	Live tissue		60 (± 5)	2
Negative control 3	Live tissue		240 (± 5)	2
Positive control	Live tissue	Glacial acetic acid	240 (± 5)	2
Test item 1	Live tissue	Farmed Bauxite Residue, Q3 2020	3	2
Test item 2	Live tissue		60 (± 5)	2
Test item 3	Live tissue		240 (± 5)	2

Additional controls

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Test item 1 *	Killed tissue	Farmed Bauxite Residue, Q2 2020	3	2
Test item 2 *			60 (± 5)	2
Test item 3 *			240 (± 5)	2
Negative control 1 *	Killed tissue	0.9% NaCl or distilled water	3	2
Negative control 2 *			60 (± 5)	2
Negative control 3 *			240 (± 5)	2
Test item without MTT 1 §	Killed tissue	Farmed Bauxite Residue, Q3 2020	3	2
Test item without MTT 2 §			60 (± 5)	2
Test item without MTT 3 §			240 (± 5)	2
Test item without MTT 1 °	Live tissue	Farmed Bauxite Residue, Q3 2020	3	2
Test item without MTT 2 °			60 (± 5)	2
Test item without MTT 3°			240 (± 5)	2

* to be added in case of test items able to reduce MTT (killed tissue will be of the same batch but the batch will be different from the alive tissue batch).
° to be added in case of test items able to stain tissue or with a potential to stain tissue.
§ to be added in case of test items able both to stain tissue and reduce MTT.

Additional experiments could be performed if necessary.

5.3.2 Treatment procedure

A sufficient amount of the test or control item (50 ± 3 µL if liquid, 20 ± 2 mg if solid, 50 ± 2 mg if waxy/sticky) will be applied to uniformely cover each epidermis surface while avoiding an infinite dose. This will allow a surface exposure of approximately 131.6 µL or mg/cm^2 (liquid or waxy/stixy substances) or 52.6 mg/cm^2 (solid substances) being the treatment area of the commercial test system equal to 0.38 cm^2. Only for solid chemicals, the epidermis surface will be moistened with 100 ± 5 µL of 0.9% NaCl solution after application of the test item. Waxy/sticky test items will be added on each single tissue with a nylon mesh, if necessary.
The exposure time will be allowed in a ventilated cabinet at room temperature. For peculiar test items (e.g. surfactant and viscous liquids), an intermediate re-spreading will be carried out, if necessary.
Each tissue will then be rinsed with approximately 25 mL of sterile PBS filling and empting the tissue insert. The excess liquid will be carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of pre-warmed maintenance medium.

5.3.3 MTT Assay

The tissue inserts and controls will be incubated with 2 mL/well of MTT ready to use solution with the exception of treated tissues without MTT which will be incubated with SkinEthic Maintenance Medium.

Plates will be incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity.
At the end of the incubation period, tissues will be placed on absorbent paper to dry. A total biopsy will be carried out by means of a specific biopsy punch supplied by SkinEthic to allow biopsies of the same dimensions. The epidermis will be separated from the collagen matrix and will both be placed in a microtube prefilled with 500 µl of acidic isopropanol. In the case of coloured collagen, unstained and untreated collagen matrices taken from killed epidermis may substitute the coloured collagen.
Tubes will be mixed by vortexing and preserved overnight at room temperature to allow formazan extraction.
At the end of the extraction period, debris will be eliminated by short centrifugation of the tubes (e.g. at 10000-14000 rpm for 2 minutes).
Aliquots of 200 µl from each sample will be read in duplicate for their absorbance at 595 nm. Optical Density (OD) values will be recorded.
On the day of the analysis, the spectrophotometer will be verified against standard solutions of MTT formazan prepared in acidic isopropanol, in order to verify if the OD values fall in the linearity range of the spectrophotometer.

5.3.4 Special procedures for control wells

Control for potentially tissue-staining test items (killed/alive epidermis)
SkinEthic Assay Medium will be added to the test item-treated well instead of MTT solution. All other procedures will be carried out as described for the main assay.

Water killed epidermis control
Before use, tissues will be thawed by incubation at room temperature with 2 mL of SkinEthic Maintenance Medium for at least one hour. All other procedures will be carried out as described for the Main Assay.

6. EVALUATION OF RESULTS

6.1 Study acceptability criteria

Blank controls: mean OD value < 0.1
Negative controls (for each exposure time point): mean OD value ≥ 0.6 and ≤ 1.5
Positive controls: mean viability expressed as percentage of the negative control ≤ 20%
Intra-replicate variability: in the range 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

6.2 Interpretation of results and classification as corrosive

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, relative and mean relative viability values (percentage relative to the negative control) will be calculated.

Cut-off values for the endpoint of the test are established as follows:

Viability related to concurrent negative control	Classification
< 35% after 3 min exposure	**Corrosive:** • Sub-categoria 1A (optional)
≥ 35% after 3 min exposure **AND** < 35% after 60 min exposure **OR** ≥ 35% after 60 min exposure **AND** < 35% after 240 min exposure	**Corrosive:** • A combination of sub-categories 1B and 1C (optional)
≥ 35% after 240 min exposure	**Non-corrosive**

For direct MTT interacting test items, non specific MTT reduction calculation (NSMTT) relative to the Negative Control will be evaluated as follows:

$$NSMTT = 100 \times \frac{OD_{\text{treated killed tissues}} - OD_{\text{non-treated killed tissues}}}{OD_{\text{negative control living tissues}}}$$

The NSMTT control per exposure time will be performed concurrently to the testing of the coloured test item.
If the NSMTT ≤ 5% only blank subtraction will be carried out.
If 5% < NSMTT ≤ 50% blank and appropriate background subtraction will be carried out.
If NSMTT > 50% results should be taken with caution.

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control will be evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{\text{test item (not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

The NSC_{living} control per exposure time will be performed concurrently to the testing of the coloured test item and in case of multiple testing, an independent NSC control will be conducted with each test performed (in each run).
If the $NSC_{living} \leq 5\%$ only blank subtraction will be carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction will be carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

For test items able both to stain tissue and reduce MTT, to avoid a possible double correction for colour interference, a third control for Non Specific Colour in killed tissues (NSC_{killed}) will be evaluated per exposure time:

$$NSC_{killed} = 100 \times \frac{OD_{\text{test item (treated killed tissues not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

If the $[(NSMTT + NSC_{living}) - NSC_{killed}] \leq 5\%$ this value will not be considered for the final calculation.

If 5% < [(NSMTT + NSC_{living}) - NSC_{killed}] ≤ 50% blank subtraction and appropriate background subtraction will be carried out.
If [(NSMTT + NSC_{living}) - NSC_{killed}] > 50% results should be taken with caution.

A single NSC_{killed} control is sufficient per test item regardless of the number of independent tests/runs performed, but should be performed concurrently to the NSMTT control.

The above corrections should be applied when the mean OD value of test item treated tissues without any correction is within the linearity range of the spectrophotometer. In case of strong interference (OD values out of the linear range) the test item is not suitable for this test method.

7. REPORTING

7.1 Presentation of data

The results will be presented in the form of tables.

7.2 Interim Report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.3 Final Report

A Draft Report will be sent to the Sponsor together with the Draft Report Approval Form. With the exception of signatures, the Draft Report will contain all information and data included in the Final Report.
Comments made by the Sponsor may be incorporated and the Final Report will be issued. If comments are not received within 6 months from despatch of the Draft Report, the Final Report will be issued.
The Final Report will include the information and data required by current internationally recognised regulations. The Final Report, digitally signed or with handwritten signatures, will be issued as PDF file, searchable, bookmarked and hyperlinked, fully compliant with the standard PDF/A-1b (ISO 19005-1 Level B), suitable for long term archiving of electronic document.

7.4 Corrections or additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the Final Report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations. Prior to final archiving of the study data, a full list will be prepared of all records associated with the study.
A reserve sample of each batch of the test item will be taken and kept under the storage conditions of the bulk supply at ERBC. The reserve sample(s) of the test item will be retained within ERBC archives for a period of 10 years and then destroyed.

Any biological samples obtained for analytical measurements or similar determinations will be managed as indicated by the Sponsor in the Draft Report Approval Form or otherwise destroyed at no charge within 3 months from the issue of the Final Report.

The Final Protocol, the Final Report and electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower, where used) will be archived at ERBC.

All other specimens, raw data, records and documentation generated during the course of this study will be archived at ERBC for a period of 3 years, after which the Sponsor will be contacted for shipment or disposal of the material (expenses will be charged to the Sponsor).

9. STUDY CONDUCT

9.1 Language

English and Italian renderings of chemical names, including that of the test material will be considered to be equivalent.

9.2 Scientific decisions

The procedures described in this Protocol may not comprehensively cover all the circumstances that can arise in the assay of the test items. When the study director considers it advisable to modify the procedures described for the selection of a solvent, interpretation of the outcome of the study or other aspects of the study conduct, he/she will carefully record the decision he/she has reached and the reasoning which led to it.

9.3 Quality assurance

According to the ERBC quality assurance programme, defined in the ERBC QA SOPs, this study will be subjected to the following procedures:

- the Protocol will be inspected,
- study/process based inspections of procedures/facilities will be carried out at intervals adequate to assure the integrity of the study,
- the Report will be inspected to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to Management and Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's Representative and Regulatory Authorities.

10. RESPONSIBILITIES OF THE SPONSOR

Items which are the responsibility of the Sponsor are indicated in section 2 of this Protocol. Since full compliance with regulatory requirements may depend on the performance of these items, the Sponsor should ensure that appropriate actions are initiated or undertaken.

11. REFERENCES

United Nations (UN) (2005). Globally Harmonised System of Classification and Labelling of Chemicals (GHS), First revised edition, UN New York and Geneva 2005.

ECVAM Protocol for EPISKIN™: an In Vitro Assay for Assessing Dermal Corrosivity Standard Operating Procedure (October 2000).

ICCVAM Evaluation of EPISKIN™, EpiDerm™ (EPI-200), and the Rat Skin Transcutaneous Electrical Resistance (TER) Assay: In Vitro test methods for Assessing Dermal Corrosivity Potential of Chemicals (NIH Publication No: 02-4502).

INVITTOX Protocol No. 118 EPISKIN™ Skin Corrosivity Test.

Version 20/1

PROTOCOL APPROVAL PAGE

for

ERBC S.r.l.

VERIFIED BY : _____ 30 Jun 2021
S. Cinelli, Biol.D., ERT — Date
Management Representative,
Associate Scientific Director,
Head of Genetic Toxicology & Alternative Methods

APPROVED BY : _____ 30 Jun 21
L. Bisini, Biol.D. — Date
Study Director

ERBC Study Number: A4370
ERBC Enquiry Number: O2631

June 2021

Version 20/1

PROTOCOL APPROVAL PAGE

for

Aughinish Alumina Ltd.

AUTHORISED BY : _____ 06/07/2021
Date

Name and Title* : RORY O'DWYER SENIOR ENVIRONMENTAL ENGINEER

* Please print or type your name and company status below your signature.

THE
NON-CLINICAL
ENGINE

EUROPEAN RESEARCH BIOLOGY CENTER

Farmed Bauxite Residue, Q4 2020

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL

(EPISKIN™/MTT method)

FINAL REPORT

ERBC STUDY NO. A4248

Sponsor:
Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

COMPLIANCE STATEMENT

I, the undersigned, was responsible for the preparation of this report and hereby declare that it constitutes a true and faithful account of the procedures adopted and of the results obtained in the performance of the study. The aspects of the study conducted by European Research Biology Center S.r.l. were performed in accordance with:

1. Decreto Legislativo 2/3/2007 n. 50, Attuazione delle direttive 2004/9/CE e 2004/10/CE, concernenti l'ispezione e la verifica della Buona Pratica di Laboratorio (BPL) ed il ravvicinamento delle disposizioni legislative, regolamentari ed amministrative relative all'applicazione dei principi di Buona Pratica di Laboratorio ed al controllo della loro applicazione per le prove sulle sostanze chimiche (G.U. 13/4/2007, Serie generale n. 86) and subsequent revisions.
2. Directive 2004/10/EC of European Parliament and of the Council of 11 February 2004, on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances.
3. ENV/MC/CHEM(98)17 OECD principles on Good Laboratory Practice (as revised in 1997).

DIGITAL SIGNATURE

L. Bisini, Biol.D.
STUDY DIRECTOR

Date

KEY STUDY STAFF

L. Bisini	Study Director
R. Zanier	Head of Quality Assurance
S. Cinelli	Associate Scientific Director, Head of Genetic Toxicology & Alternative Methods

Test Facility Management

S. Venturella, Biol.D., ERT	Test Facility Director

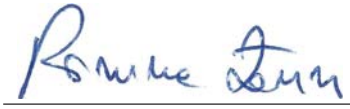
QUALITY ASSURANCE STATEMENT

Study phases	Inspection dates	Report to SD[a]	Report to CM[b]
Study Plan			
Study Plan check	11.02.2021	11.02.2021	11.02.2021
Process based inspections related to this type of study			
Dose preparation	18.01.2021	-	03.03.2021
Test execution	11.11.2020	-	13.11.2020
Final Report (end of review)	*date of QA Statement signature*		

[a] *SD = Study Director only for protocol check and study based inspections*
[b] *CM = Company Management*

Other QA process based inspections were carried out on departments or laboratories performing routine activities (e.g. Analytical Chemistry, Histopathology, Veterinary Services and Clinical Pathology) as well as on other routine activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here. Involved departments or laboratories and support functions are also subject to regular facility inspections.

Review of this report by ERBC QA found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.



7th September 2021

R. Zanier, CMB, Ph.D.
HEAD OF QA

Date

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1 SUMMARY

The potential of the test item Farmed Bauxite Residue, Q4 2020 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™. The experimental procedures are based on the OECD Guideline for testing of chemicals no. 431. The test item, as well as controls, were tested for their ability to impair cell viability after an exposure period of 3, 60 and 240 minutes. The final endpoint of the assay is the colorimetric measurement of MTT reduction (blue formazan salt) in the test system, being this reaction an index of cell viability. The test item was tested as supplied by the Sponsor.

A preliminary test was carried out to evaluate the compatibility of the test item with the test system. In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Therefore, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

In the Main Assay, for each treatment time, the test item (physical state: solid) was applied as supplied in two replicates, at the treatment level of 20±2 mg/*epidermis* unit, each measuring 0.38 cm^2 (treatment level: 52.6 mg/cm^2). Positive and negative controls (Glacial acetic acid and Physiological saline, respectively) were concurrently tested, in the same number of replicates and test conditions at the treatment level of 50 µL/*epidermis* unit. Positive control was included only at the longest treatment time of 240 minutes, while a negative control was included for each treatment time.

In the Main Assay, the negative controls gave the expected baseline value (Optical Density values ≥ 0.6 and ≤ 1.5) and variability (difference of viability between the two replicates lower than 30%), at each treatment time, in agreement with the guideline indications. For each treatment time, the concurrent negative control mean value is considered the baseline value of the treatment series and thus represents 100% of cell viability.

The positive control caused the expected cell death (0% of cell viability, when compared to the negative control).

Based on the stated criteria, the assay was regarded as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after treatment with the test item, at all treatment time. The mean cell viability was equal to or higher than 35% at all treatment times. Each mean cell viability, after the concurrent blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	50
60	45
240	35

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2020 is identified as non-corrosive to the skin.

2 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the potential skin corrosion of the test item as measured by its ability to induce cell death in a commercial reconstructed human epidermis (RhE) model, EPISKIN™.

2.2 Regulatory compliance

Experimental procedures were based on the following guideline:

- OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method" (Adopted on 18 June 2019).

The Sponsor affirmed that the test item is a chemical product (industrial waste) and that the study was performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

2.3 Principle of the test

The test system EPISKIN™ is a reconstructed human epidermis (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.*, the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the stratum corneum by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue; CAS N. 298-93-1] into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2.4 Sponsor and Test Facility

The study was performed at:

European Research Biology Center S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

On behalf of the Sponsor:

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

2.5 Study schedule

Procedure	**Date**
Protocol approved by: Study Director	09 February 2021
Start of experimental phase Preliminary test	11 February 2021
End of experimental phase Completion of scoring of Main Assay	26 February 2021
Study completion	Date of Study Director's signature on this report

3 TEST ITEM AND CONTROL ITEMS

3.1 Test Item

3.1.1 Identity

Details of the test item received at ERBC were as follows:

Identity	Farmed Bauxite Residue, Q4 2020
Label name	Farmed Bauxite Residue
Batch no.	Q4 2020
Expiry date	January 2023
Storage conditions	Room temperature
ERBC no.	17298

The determination of the identity, strength, purity, composition and stability of the test item and the quality system under which the test item characterisation was performed was the responsibility of the Sponsor. The certificate of analysis is presented in Addendum 1 of this report. A sample of test item was taken and will be stored in the archives of ERBC for 10 years prior to disposal.

3.2 Control Items

Positive control item was Glacial acetic acid (C. Erba, batch no. P6NO24277B).

Negative control item was Physiological saline (Baxter, batch no. 19H0603).

Positive and negative control items were obtained commercially and characterised by labelling. Determination of the stability and concentration of solutions of positive and negative controls were not undertaken, since it is sufficient to provide evidence for the correct expected response of the test system to them.

4 METHODS

4.1 Test System

4.1.1 EPISKIN™

Commercial Name	EPISKIN™ - 0.38 cm^2
Supplier	SkinEthic Laboratories (4, A. Fleming – 69366 Lyon – France)
Batch	21-EKIN-008
Arrived at ERBC on	24 February 2021

Functional controls

Quality controls: histology scoring, magnitude of viability and barrier function (IC_{50} determination).

Biological safety: absence of HIV1 and 2 antibodies, hepatitis C antibodies, hepatitis B antigen HBs, absence of bacteria, fungi and mycoplasma.

A certificate of analysis can be found in Addendum 2.

4.1.2 Preparation of the Test System

Examination at arrival

Temperature indicator: pale grey (suitable for use)

pH indicator: orange (suitable for use)

Preparation and pre-treatment incubation period

According to the supplier procedure, at arrival, plates were opened under a sterile airflow and each insert, containing the epidermal tissue, was carefully taken out and placed in a 12-well plate in which each well had previously been filled with 2 mL/well SkinEthic Maintenance Medium. Culture plates were placed in the incubator at 37°C, 5% CO_2 and saturated humidity for approximately 24 hours.

4.2 Media

Maintenance Medium	SkinEthic; batch: 21-MAIN3-008
Assay Medium	SkinEthic; batches: 21 ESSC 006 and 21 ESSC 008

4.3 Experimental procedure

4.3.1 Preliminary test

Direct MTT reduction test (Step 1)

Non-specific reduction of MTT was evaluated as follows: two mL of MTT ready-to-use solution (0.3 mg/mL) was incubated with 20±2 mg of test item at 37 °C, 5% CO_2 and saturated humidity for 3 hours, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time was carried out.

Colouring potential test (Step 2)

Chemicals' colouring potential was assessed for potential interaction with the test system. 10±1 mg of test item was added to 90 µL of distilled water (Eurospital; batch no. 20C3004) in a transparent tube and the resulting solution/suspension mixed by using a vortex for 15 minutes. Colouring of the solution/suspension at the end of the incubation time was evaluated by unaided eye.

4.3.2 Main Assay

Treatment

In Main Assay, alive tissues were treated with the test item, positive and negative controls. The treatment scheme was the following:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Negative control	Live tissue	Physiological saline	3	50 µL	2	CN1A, CN1B
Negative control	Live tissue	Physiological saline	60	50 µL	2	CN2A, CN2B
Negative control	Live tissue	Physiological saline	240	50 µL	2	CN3A, CN3B
Positive control	Live tissue	Glacial acetic acid	240	50 µL	2	CP1A, CP1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2020	3	20±2 mg	2	TI-B1A, TI-B1B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2020	60	20±2 mg	2	TI-B2A, TI-B2B
Test item	Live tissue	Farmed Bauxite Residue, Q4 2020	240	20±2 mg	2	TI-B3A, TI-B3B

Additional controls were included in the Main Assay with the following treatment scheme:

Sample	Test System	Treatment	Treatment time (minutes)	Amount per well	Number of replicates	Sample code
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2020	3	20±2 mg	2	CC-B1A, CC-B1B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2020	60	20±2 mg	2	CC-B2A, CC-B2B
Test item without MTT	Live tissue	Farmed Bauxite Residue, Q4 2020	240	20±2 mg	2	CC-B3A, CC-B3B

Exposure period

Exposure times of 3, 60±5 and 240±5 minutes were allowed in a ventilated cabinet at room temperature.

Washing

At the end of the exposure, each tissue was rinsed with approximately 25 mL of sterile PBS, filling and empting the tissue insert. The excess liquid was carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of maintenance medium.

MTT staining

Each tissue insert was incubated with 2 mL/well of MTT ready-to-use solution. Plates were incubated for 3 hours ± 5 minutes at 37°C, 5% CO_2 and saturated humidity. At the end of the incubation period, tissues were placed on absorbent paper to dry. A total biopsy was carried out by means of a biopsy punch to allow biopsies of the same dimensions.

The epidermis were separated from the collagen matrix and both placed in a microtube prefilled with 500 µL of acidic isopropanol. Tubes were mixed by vortexing and preserved overnight at room temperature to allow formazan extraction. At the end of the extraction period, debris were eliminated by short centrifugation of the tubes (14000 rpm for 2 minutes) and aliquots of 200 µL from each sample were read in duplicate for their absorbance at 595 nm. Six aliquots (200 µL) of acidic isopropanol were analysed and used as blank. An MTT formazan calibration curve was performed in order to ensure that OD values obtained in the main experiment were within the spectrophotometer linear range.

4.4 Analysis and evaluation of data

4.4.1 Study Acceptability Criteria

The assay was considered valid if the following criteria were met:

- Blank controls: mean OD value < 0.1.
- Negative controls: mean OD value ≥ 0.6 and ≤ 1.5, difference of viability between the two replicates ≤ 30%.

- Positive controls: mean viability expressed as percentage of the negative control ≤ 20%.
- In the range of 20-100% viability and for ODs ≥ 0.3, difference of viability between the two replicate cultures treated with the test item ≤ 30%.

4.4.2 Interpretation of results and classification

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, mean relative viability values (percentage relative to the concurrent negative control) were calculated.

Cut-off values for the endpoint of the test are established as follows:

Criteria	Classification
< 35% after 3 min exposure	Corrosive Sub-categoria 1A
≥ 35% after 3 min exposure AND < 35% after 60 min exposure OR ≥ 35% after 60 min exposure AND < 35% after 240 min exposure	Corrosive: combination of sub-categories 1B and 1C
≥ 35% after 240 min exposure	Non- Corrosive

For colouring test items, Non Specific Colour (NSC_{living}) relative to the D-PBS Control is evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{test\ item(not\ incubated\ with\ MTT)}}{OD_{negative\ control\ living\ tissues}}$$

If the $NSC_{living} \leq 5\%$ only blank subtraction is carried out.

If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction is carried out.

If $NSC_{living} > 50\%$ results should be taken with caution.

4.5 Protocol deviations

No deviation occurred during the study.

4.6 Archives

Full records of all aspects of the study conduct were maintained together with the results of all measurements and observations. All specimens, raw data, records and documentation generated during the course of this study will be retained within ERBC archives. The data will be kept for a period of 3 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material. The Final Protocol, the Final Report and, where applicable, electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower), will be archived at ERBC.

5 RESULTS

5.1 Preliminary test

Before the Main Assay, a preliminary test was carried out to evaluate the compatibility of the test item with the test system. Results of this preliminary test can be found in Table 1.

In a first step, the test item was assayed for the ability of reducing MTT *per se*. A red/brown suspension with a brown precipitate was observed. However, this change was attributed to the colour of the substance and not to a non-specific reduction of MTT. Thus no additional controls were added in the main phase for the evaluation of MTT non-specific reduction. In a second step, the test item was assayed for the ability of colouring water *per se*. A brown suspension was obtained. Thus, in order to avoid any misinterpretation due to the colouring interference, an additional control for the evaluation of Non Specific Colouring potential (NSC_{living}) was added in the Main Assay.

5.2 Main Assay

A Main Assay was performed. Raw data and data elaboration are reported in Table 2.

The mean Optical Density of Blank Controls was 0.037, lower than the maximum acceptable value (0.1). All negative control mean OD values gave the expected baseline value and variability, in agreement with guideline indications. According to the method, each negative control mean value is considered the baseline value for the concurrent treatment series, thus they represent 100% of cell viability.

Positive control results indicated an appropriate cell death with an acceptable relative cell viability (0% of the negative control value).

Based on the stated criteria, the study was accepted as valid.

The NSC_{living} values were lower than 5% at all treatment times, thus only the OD-blank background subtraction was performed.

Reduction of cell viability was observed after treatment with the test item, at all treatment time. However, the mean percent viabilities were not reduced below 35% of the concurrent negative control, at any treatment time. Each mean cell viability, after the blank subtraction, was as follows:

Treatment time (minutes)	Mean cell viability (%)
3	50
60	45
240	35

Intra-replicate variability was acceptable with a difference of viability between the two replicates lower than 30%, for all treatment times.

Based on the results obtained, the test item Farmed Bauxite Residue, Q4 2020 is identified as non-corrosive to the skin.

6 CONCLUSION

The potential of the test item Farmed Bauxite Residue, Q4 2020 to be corrosive to the skin was investigated through an *in vitro* skin corrosion study, using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.

The blank, negative and positive controls gave acceptable results at all treatment times, thus the study was accepted as valid.

The mean cell viability of the test item treated tissues, after the blank subtraction, was equal to or higher than 35% at all treatment times. Based on these results, the test item Farmed Bauxite Residue, Q4 2020 is identified as non-corrosive to the skin.

7 TABLES

Farmed Bauxite Residue, Q4 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN^{TM}/MTT method)

STUDY NO.: A4248

PRELIMINARY TEST

Direct MTT reduction test (Step 1)

Test item (mg)	**MTT ready to use solution (mL)**	**Container**	**Incubation condition**	**Colour Observation**
20 ± 2	2.0	well	3 h at 37°C, 100% nominal humidity 5% CO_2	Red/brown suspension, with brow precipitate (no interaction)

Colouring potential test (Step 2)

Test item (mg)	**Water (µL)**	**Container**	**Incubation condition**	**Colour Observation**
10 ± 1	90	Eppendorf tube	15', ambient condition, in agitation	Brown suspension (possible interaction)

Farmed Bauxite Residue, Q4 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4248

MAIN ASSAY

TREATMENT TIME: 3 minutes

BLANK		**Negative Control**						
	OD_{blank}					**OD_{NC}**		**Viability (%)**
	0.0365	CN1A-1	1.0623	1.0257		0.9330		100.3
	0.0367	CN1A-2	0.8769	0.8403				
	0.0365	CN1B-1	0.9171	0.8805		0.9274		99.7
	0.0369	CN1B-2	1.0110	0.9744				
	0.0365							
	0.0366							
Mean	0.037	**Mean**		0.930	**Mean**	0.930		100
SD	0.0002	**SD**		0.085				
CV(%)	0.44	**CV(%)**		9.1			**Δ (%)**	0.6

Test Item						
				OD_{TI}		**Viability (%)**
TI-B1A-1	0.4703	0.4337		0.4559		49.0
TI-B1A-2	0.5148	0.4782				
TI-B1B-1	0.5185	0.4819		0.4820		51.8
TI-B1B-2	0.5188	0.4822				
Mean		0.469	**Mean**	0.469		**50**
SD		0.024				
CV(%)		5.0			**Δ (%)**	5.6

Test Item without MTT						
				ODcc		**NSCliving (%)**
CC-B1A-1	0.0411	0.0045		0.0024		0.3
CC-B1A-2	0.0369	0.0003				
CC-B1B-1	0.0387	0.0021		0.0050		0.5
CC-B1B-2	0.0445	0.0079				
Mean		0.004	**Mean**	0.004		**0**
SD		0.003				
CV(%)		89.2			**Δ (%)**	70.6

Farmed Bauxite Residue, Q4 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4248

MAIN ASSAY

TREATMENT TIME: 60 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0365	CN2A-1	1.0669	1.0303		1.0011	93.8
	0.0367	CN2A-2	1.0085	0.9719			
	0.0365	CN2B-1	1.2682	1.2316		1.1345	106.2
	0.0369	CN2B-2	1.0741	1.0375			
	0.0365						
	0.0366						
Mean	0.037	**Mean**		1.068	**Mean**	1.068	100
SD	0.0002	**SD**		0.113			
CV(%)	0.44	**CV(%)**		10.6		**Δ (%)**	12.5

Test Item					
				OD_{TI}	**Viability (%)**
TI-B2A-1	0.5399	0.5033		0.4881	45.7
TI-B2A-2	0.5096	0.4730			
TI-B2B-1	0.5128	0.4762		0.4734	44.3
TI-B2B-2	0.5073	0.4707			
Mean		0.481	**Mean**	0.481	**45**
SD		0.015			
CV(%)		3.2		**Δ (%)**	3.1

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B2A-1	0.0553	0.0187		0.0120	1.1
CC-B2A-2	0.0420	0.0054			
CC-B2B-1	0.0408	0.0042		0.0045	0.4
CC-B2B-2	0.0414	0.0048			
Mean		0.008	**Mean**	0.008	**1**
SD		0.007			
CV(%)		84.4		**Δ (%)**	91.4

Farmed Bauxite Residue, Q4 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4248

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0365	CN3A-1	1.3327	1.2961		1.1815	100.8
	0.0367	CN3A-2	1.1036	1.0670			
	0.0365	CN3B-1	1.2565	1.2199		1.1627	99.2
	0.0369	CN3B-2	1.1422	1.1056			
	0.0365						
	0.0366						
Mean	0.037	**Mean**		1.172	**Mean**	1.172	100
SD	0.0002	**SD**		0.105			
CV(%)	0.44	**CV(%)**		9.0		**Δ (%)**	1.6

Test Item					
				OD_{TI}	**Viability (%)**
TI-B3A-1	0.4566	0.4200		0.4155	35.5
TI-B3A-2	0.4477	0.4111			
TI-B3B-1	0.4433	0.4067		0.4151	35.4
TI-B3B-2	0.4601	0.4235			
Mean		0.415	**Mean**	0.415	**35**
SD		0.008			
CV(%)		1.9		**Δ (%)**	0.1

Test Item without MTT					
				ODcc	**NSCliving (%)**
CC-B3A-1	0.0507	0.0141		0.0129	1.1
CC-B3A-2	0.0484	0.0118			
CC-B3B-1	0.0617	0.0251		0.0164	1.4
CC-B3B-2	0.0443	0.0077			
Mean		0.015	**Mean**	0.015	**1**
SD		0.007			
CV(%)		50.7		**Δ (%)**	23.5

Farmed Bauxite Residue, Q4 2020
IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

STUDY NO.: A4248

MAIN ASSAY

TREATMENT TIME: 240 minutes

BLANK		**Negative Control**					
	OD_{blank}					**OD_{NC}**	**Viability (%)**
	0.0365	CN3A-1	1.3327	1.2961		1.1815	100.8
	0.0367	CN3A-2	1.1036	1.0670			
	0.0365	CN3B-1	1.2565	1.2199		1.1627	99.2
	0.0369	CN3B-2	1.1422	1.1056			
	0.0365						
	0.0366						
Mean	0.0366	**Mean**		1.172	**Mean**	1.172	100.0
SD	0.0002	**SD**		0.105			
CV(%)	0.44	**CV(%)**		9.0		**Δ (%)**	1.6

Positive control					
				OD_{TI}	**Viability (%)**
CP1A-1	0.0381	0.0015		0.0014	0.1
CP1A-2	0.0380	0.0014			
CP1B-1	0.0380	0.0014		0.0017	0.1
CP1B-2	0.0387	0.0021			
Mean		0.002	**Mean**	0.002	**0.1**
SD		0.000			
CV(%)		21.3		**Δ (%)**	18.95

8 ADDENDA

RUSAL
AUGHINISH

Aughinish Alumina Ltd.
Aughinish Island
Askeaton
Co. Limerick
IRELAND

CERTIFICATE OF ANALYSIS

Sample Type : Farmed bauxite residue
Sample mass : 10g (approx.) per sample
Report Issued : 12/03/2021

Sample	% Moisture	Units	Method
Farmed Bauxite Residue, Q2 2019	27.5	%w/w	ATM047
Farmed Bauxite Residue, Q4 2019	23.0	%w/w	ATM047
Farmed Bauxite Residue, Q1 2020	24.0	%w/w	ATM047
Farmed Bauxite Residue, Q4 2020	21.4	%w/w	ATM047

Jason Clohessy

LABORATORY QUALITY MANAGER
Jason Clohessy

"This report relates only to the items tested and shall not be reproduced except in full and with the approval of the Laboratory of Aughinish Alumina Ltd".

EPISKIN

TECHNICAL DATA, SAFETY SHEET AND CERTIFICATE OF ANALYSIS

CCE-091-SM D13-S/04

NAME

EpiSkin™ Small / Human Epidermis (SM/13)

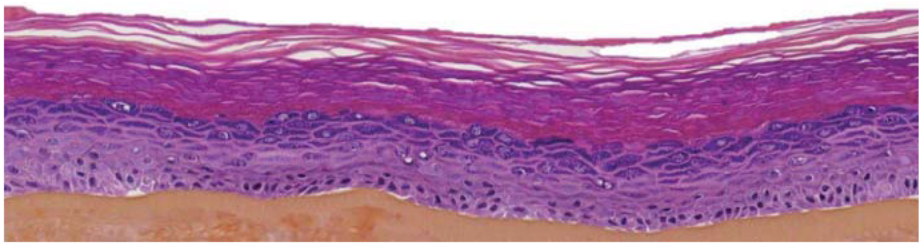
DESCRIPTION

0.38 cm² reconstructed epidermis of normal human keratinocytes. Cells are grown on a collagen matrix, for 13 days

BATCH : **21-EKIN-008**
ORIGIN : Adult donors
USAGE : FOR SCIENTIFIC USE ONLY - PRODUCT OF HUMAN ORIGIN
STORAGE : This product was prepared and packaged using aseptic techniques. Store in an incubator at 37°C, 5% CO2 with saturated humidity

QUALITY CONTROLS

Control # E210203

	Process	Specification	Result
HISTOLOGY	HES stained paraffin section	Multi-layered, highly differentiated epidermis consisting of organized basal, spinous and granular layers, and a multilayered *stratum corneum*	**Satisfactory**
		Number of cell layers ≥ 4	**7 cell layers**
			
IC50 DETERMINATION	SDS concentration, MTT test.	1.5 mg/mL ≤ IC50 ≤ 3.0 mg/mL	**2.2 mg/mL**

BIOLOGICAL SAFETY:

On blood of the donors, we have verified the absence of HIV1 and 2 antibodies, hepatitis C antibodies and hepatitis B antigen HBs.
On cells from the donors, we have verified the absence of bacteria, fungus and mycoplasma.

SUGGESTED EXPIRATION DATE:

March 1, 2021

Lyon, February 23, 2021
Certified and released by Anaïs JENSEN, Quality Control Manager

Manufactured in accordance to the ISO9001 quality system of Episkin.

The use of this human tissue is strictly limited to *in vitro* testing. All other manipulations of this tissue such as: extraction and maintenance of single cells in culture, use of the tissue for diagnostic or therapeutic purposes and in human subjects, are strictly prohibited.

THE
NON-CLINICAL
ENGINE
EUROPEAN RESEARCH BIOLOGY CENTER

Version 20/2

Farmed Bauxite Residue, Q4 2020
***IN VITRO* SKIN CORROSION STUDY USING A**
RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL
(EPISKIN™/MTT method)

Final Protocol
prepared for

Aughinish Alumina Ltd.
Aughinish island, Askeaton
Co. Limerick
Ireland

by

EUROPEAN RESEARCH BIOLOGY CENTER S.r.l.
Via Tito Speri, 12/14
00071 Pomezia
Italy

ERBC Study Number: A4248
ERBC Enquiry Number: O1788

February 2021

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www.erbc-group.com

IN VITRO SKIN CORROSION STUDY USING A RECONSTRUCTED HUMAN EPIDERMIS (RhE) MODEL (EPISKIN™/MTT method)

MANAGEMENT OF STUDY

Study Director	:	L. Bisini, Biol.D. lbisini@erbc-group.com
Sponsor	:	Aughinish Alumina Ltd. Aughinish island, Askeaton Co. Limerick Ireland
Monitor	:	R. O'Dwyer

QUALITY ASSURANCE

Head of QA & GXP Compliance	:	R. Zanier, CMB, PhD

LOCATION OF STUDY

The study will be performed at	:	European Research Biology Center S.r.l. Via Tito Speri, 12/14 00071 Pomezia Italy

The laboratory facilities, archives and administration are located at this site.

PROJECTED TIME PLAN

			Date
1.	Proposed experimental starting date	:	First half of February 2021
2.	Proposed experimental completion date	:	2 weeks from the start of the experimental phase
3.	QA-Audited Draft Report to Sponsor	:	2 weeks after the end of the experimental phase

Any change in the experimental design or any additional activity requested to maintain the scientific or regulatory integrity of the study might cause a change in time schedule indicated above.

1. INTRODUCTION

1.1 Objective

This test allows the identification of non-corrosive and corrosive substances and mixtures in accordance with the UN GHS (1). The test system EPISKIN™ is one of the available commercial reconstructed human *epidermis* (RhE) models used for distinguishing corrosive (C) from non-corrosive (NC) substances. It further supports the sub-categorization of corrosive substances and mixtures into optional Sub-category 1A, in accordance with the UN GHS, as well as a combination of Sub-categories 1B and 1C.

1.2 Regulatory requirements

This study will be conducted in compliance with the GLP regulations of:

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004;
- ENV/MC/CHEM(98)17 "OECD principles on Good Laboratory Practice – as revised in 1997";
- Decreto Legislativo no. 50 of 2 March 2007 and subsequent revisions.

The Sponsor has affirmed that the test item is a chemical product (industrial waste) and that the study will be performed to comply with the relevant legislation for safety assessment, for notification or for submission to Regulatory Authorities.

In addition, the study is designed to comply with the experimental methods indicated in the guidelines of:

OECD Guideline for the testing of chemicals no. 431 "*In Vitro* Skin Corrosion: Reconstructed Human Epidermis (Rhe) Test Method" (Adopted on 18 June 2019);

1.3 Principles of the method

The test system EPISKIN™ is a reconstructed human *epidermis* (RhE) model, which in its overall design (the use of human derived *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.,* the *epidermis*.

The principle of the RhE test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Cell viability is measured by dehydrogenase conversion of the vital dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, thiazolyl blue], into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identified by their ability to decrease cell viability below defined threshold levels.

2. TEST ITEM

2.1 Characterisation

It will be the responsibility of the Sponsor to determine, for each batch of test item the identity, strength, purity and composition, or other characteristics which appropriately define the test item, before its use in the study. The determination of the stability of the test item and the quality system under which the test item characterisation was performed will also be the Sponsor's responsibility.
A certificate of analysis for the test item should be supplied.

2.2 Identity

The test item will be Farmed Bauxite Residue, Q4 2020.

The following information, supplied by the Sponsor, refers to the original batch of test item received for the study:

Batch number: Q4 2020
Expiry date: not available
Storage conditions: room temperature

Should further batches be required to complete the study, full details of batch usage will be maintained in the formulation records but protocol amendments will not be issued.
The amount of the test item received and used will be recorded according to standard procedures.

2.3 Preparation of test item

Test item will be used in the form supplied.
If necessary, solid substances will be ground to reduce particle size and aid suspension.

2.4 Safety precautions

The precautions necessary when handling the test item are based on information supplied by the Sponsor. The minimum safety precautions necessary are detailed under ERBC Hazard Classification System, according to ERBC standard procedures.

2.5 Disposal

Approximately 1 year after the Final Report has been issued, remaining amounts of the test item, with the exception of the reserve samples taken for archival purposes, will be destroyed by incineration or returned to the Sponsor.

3. CONTROL ITEMS

3.1 The control items are commercially obtained by ERBC. Information about the identity, strength, purity and composition or other characteristics appropriately defining these compounds, before their use in the study, as well as the stability are detailed in documents obtained from the Supplier.

3.2 Control items will be the following:
- Negative control: The preferred choice will be 0.9% (w/v) NaCl, but Distilled Water (Bieffe Medital or equivalent) can be used, if necessary.
- Positive control item: Glacial Acetic Acid.

Determination of the stability and concentration of solutions of these agents will not be undertaken since it is sufficient to provide evidence of the correct expected response of the test system to them.

4. MATERIALS AND METHODS

4.1 EPISKIN™

The test system EPISKIN™ is commercially available from SkinEthic Laboratories.

4.1.1 Characteristic of the test system

The SkinEthic reconstructed human tissue model EPISKIN™ consists of an airlifted, living, multi-layered tissue construct, produced in polycarbonate inserts in serum-free and chemically defined medium, featuring normal ultra-structure and functionality equivalent to human tissue *in vivo*.
Normal human keratinocytes are used to reconstruct the epithelium. Multiple layers of viable epithelial cells (basal layer, *stratum spinosum, stratum granulosum*) should be present under a functional *stratum corneum*. *Stratum corneum* should be multilayered containing the essential lipid profile to produce a functional barrier with robustness to resist rapid penetration of cytotoxic marker chemicals.

4.1.2 Functional conditions

The barrier function should be demonstrated. The containment properties of the RhE model should prevent the passage of material around the *stratum corneum* to the viable tissue, which would lead to poor modelling of skin exposure.
The RhE model supplier should ensure that each batch of the RhE model used meets defined production release criteria. A certificate will be supplied for each batch of the test system.

4.1.3 Preparation and storage of the test system

Immediately after arrival, the multiwell plate will be opened under a sterile airflow. Each insert containing the epidermal tissue will be carefully taken out. Any remaining agarose that adheres to the outer sides of the insert will be rapidly removed by gentle blotting on the sterile filter paper. Inserts will be quickly placed in a 12-well plate in which each well has previously been filled with 2 mL/well SkinEthic Maintenance Medium (pre-warmed at 37 °C) making sure that no air bubbles are formed underneath the inserts.
Culture plates will be placed in the incubator at 37°C, 5% CO_2 and saturated humidity.
Testing can initiate after at least two hours of incubation.

4.2 Media and reagents

SkinEthic Maintenance Medium Supplied with the EPISKIN™
To be stored at 2-8°C. To be used at room temperature (without pre-heating).

SkinEthic Assay Medium To be stored at 2-8°C.	Supplied with the EPISKIN™
0.9% (w/v) NaCl	
Glacial Acetic Acid	
MTT Stock Solution	3 mg/mL MTT in D-PBS.
MTT Ready-to-use Solution	MTT Stock Solution diluted 1:10 (v/v) with pre-warmed SkinEthic Assay Medium (final concentration 0.3 mg/mL of MTT).
Acidic Isopropanol	0.04 N HCl in Isopropanol
Water-killed epidermis	to be prepared only for MTT interacting reagents. Living epidermis is incubated with 2 mL of distilled water at 37°C, 5% CO_2 and saturated humidity for approximately 2 days. The water is discarded and the samples frozen at -18 to -20°C for up to 6 months.

5. EXPERIMENTAL PROCEDURE

5.1 Experimental design

Before testing the test item for corrosive properties, adequacy of the test system will be verified to ensure that the test item enters in the applicability domain of the assay.
A preliminary test will be undertaken in two steps. The test item will be checked for the ability to reduce the MTT (Step 1) and to colour water (Step 2).
The main experiment will be carried out including all controls to assess corrosive potential and classify the test item, according to the EU/GHS regulations.

5.2 Preliminary test

5.2.1 Direct MTT reduction test (Step 1)

Non-specific reduction of MTT will be evaluated as follows:
Two mL of MTT Ready-to-use Solution will be incubated with an amount of the test item (50 µL if liquid, 20 ± 2 mg if solid) and incubated at 37°C, 5% CO_2 and saturated humidity for 3 hours protected from light, simulating test conditions. Observation of blue or purple appearance of the solution at the end of the incubation time will imply the use of water killed epidermis as a control in the main assay (additional cost).

5.2.2 Colouring potential test (Step 2)

To identify potential interference by coloured test chemicals or test chemicals that become coloured when in contact with water and decide on the need for additional controls, spectral analysis of the test chemical in water should be performed.
An amount of the test item (10 µL if liquid, 10 ± 1 mg if solid) will be added to 90 µL of distilled water in a transparent tube (vial or micro-tube). The mixture will be blended for approximately 15 minutes and spectral analysis, if necessary, will be performed at 595 nm.
Colouring of the solution (e.g. observation of blue or purple appearance) at the end of the incubation time will imply the use of alive samples treated without MTT as a control in the main assay.

5.2.3 Further preliminary test (Additional cost)

When a positive result is obtained in preliminary tests described either in section 5.2.1 or 5.2.2 (or both), further preliminary test may be conducted to quantify the ability of the test item to reduce MTT or to stain tissue before beginning the main test. The results may indicate that the test item is not suitable for the test system before beginning a complete main assay. These assays will be conducted only in agreement with the Sponsor.
Otherwise, the Main Assay will be conducted with all the appropriate controls.

5.3 Main Assay

5.3.1 Treatment scheme

A Main Assay will be carried out including the test item, positive and negative controls. A typical treatment scheme may be the following:

Basic assay:

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Negative control 1	Live tissue	0.9% NaCl or distilled water	3	2
Negative control 2	Live tissue		60 (± 5)	2
Negative control 3	Live tissue		240 (± 5)	2
Positive control	Live tissue	Glacial acetic acid	240 (± 5)	2
Test item 1	Live tissue	Farmed Bauxite Residue, Q4 2020	3	2
Test item 2	Live tissue		60 (± 5)	2
Test item 3	Live tissue		240 (± 5)	2

Additional controls

Sample	Test system	Treatment	Exposure time point (mins)	Number of replicates
Test item 1 *	Killed tissue	Farmed Bauxite Residue, Q4 2020	3	2
Test item 2 *			60 (± 5)	2
Test item 3 *			240 (± 5)	2
Negative control 1 *	Killed tissue	0.9% NaCl or distilled water	3	2
Negative control 2 *			60 (± 5)	2
Negative control 3 *			240 (± 5)	2
Test item without MTT 1 §	Killed tissue	Farmed Bauxite Residue, Q4 2020	3	2
Test item without MTT 2 §			60 (± 5)	2
Test item without MTT 3 §			240 (± 5)	2
Test item without MTT 1 °	Live tissue	Farmed Bauxite Residue, Q4 2020	3	2
Test item without MTT 2 °			60 (± 5)	2
Test item without MTT 3°			240 (± 5)	2

* to be added in case of test items able to reduce MTT (killed tissue will be of the same batch but the batch will be different from the alive tissue batch).
° to be added in case of test items able to stain tissue or with a potential to stain tissue.
§ to be added in case of test items able both to stain tissue and reduce MTT.

Additional experiments could be performed if necessary.

5.3.2 Treatment procedure

A sufficient amount of the test or control item (50 ± 3 µL if liquid, 20 ± 2 mg if solid, 50 ± 2 mg if waxy/sticky) will be applied to uniformely cover each epidermis surface while avoiding an infinite dose. This will allow a surface exposure of approximately 131.6 µL or mg/cm^2 (liquid or waxy/stixy substances) or 52.6 mg/cm^2 (solid substances) being the treatment area of the commercial test system equal to 0.38 cm^2. Only for solid chemicals, the epidermis surface will be moistened with 100 ± 5 µL of 0.9% NaCl solution after application of the test item. Waxy/sticky test items will be added on each single tissue with a nylon mesh, if necessary.
The exposure time will be allowed in a ventilated cabinet at room temperature. For peculiar test items (e.g. surfactant and viscous liquids), an intermediate re-spreading will be carried out, if necessary.
Each tissue will then be rinsed with approximately 25 mL of sterile PBS filling and empting the tissue insert. The excess liquid will be carefully removed and the sample transferred in new wells pre-filled with 2 mL/well of pre-warmed maintenance medium.

5.3.3 MTT Assay

The tissue inserts and controls will be incubated with 2 mL/well of MTT ready to use solution with the exception of treated tissues without MTT which will be incubated with SkinEthic Maintenance Medium.
Plates will be incubated for 3 hours ± 15 minutes at 37°C, 5% CO_2 and saturated humidity.
At the end of the incubation period, tissues will be placed on absorbent paper to dry. A total biopsy will be carried out by means of a specific biopsy punch supplied by SkinEthic to allow biopsies of the same dimensions. The epidermis will be separated from the collagen matrix and will both be placed in a microtube prefilled with 500 µl of acidic isopropanol. In the case of coloured collagen, unstained and untreated collagen matrices taken from killed epidermis may substitute the coloured collagen.
Tubes will be mixed by vortexing and preserved overnight at room temperature to allow formazan extraction.
At the end of the extraction period, debris will be eliminated by short centrifugation of the tubes (e.g. at 10000-14000 rpm for 2 minutes).
Aliquots of 200 µl from each sample will be read in duplicate for their absorbance at 595 nm. Optical Density (OD) values will be recorded.
On the day of the analysis, the spectrophotometer will be verified against standard solutions of MTT formazan prepared in acidic isopropanol, in order to verify if the OD values fall in the linearity range of the spectrophotometer.

5.3.4 Special procedures for control wells

Control for potentially tissue-staining test items (killed/alive epidermis)
SkinEthic Assay Medium will be added to the test item-treated well instead of MTT solution. All other procedures will be carried out as described for the main assay.

Water killed epidermis control
Before use, tissues will be thawed by incubation at room temperature with 2 mL of SkinEthic Maintenance Medium for at least one hour. All other procedures will be carried out as described for the Main Assay.

6. EVALUATION OF RESULTS

6.1 Study acceptability criteria

Blank controls: mean OD value < 0.1
Negative controls (for each exposure time point): mean OD value ≥ 0.6 and ≤ 1.5
Positive controls: mean viability expressed as percentage of the negative control ≤ 20%
Intra-replicate variability: in the range 20-100% viability and for ODs ≥ 0.3, difference of viability between the two tissue replicates should not exceed 30%.

6.2 Interpretation of results and classification as corrosive

After appropriate blank subtractions and/or corrections for the background controls, means, standard deviations, coefficients of variation, relative and mean relative viability values (percentage relative to the negative control) will be calculated.

Cut-off values for the endpoint of the test are established as follows:

Viability related to concurrent negative control	Classification
< 35% after 3 min exposure	**Corrosive:** • Sub-categoria 1A (optional)
≥ 35% after 3 min exposure **AND** < 35% after 60 min exposure **OR** ≥ 35% after 60 min exposure **AND** < 35% after 240 min exposure	**Corrosive:** • A combination of sub-categories 1B and 1C (optional)
≥ 35% after 240 min exposure	**Non-corrosive**

For direct MTT interacting test items, non specific MTT reduction calculation (NSMTT) relative to the Negative Control will be evaluated as follows:

$$NSMTT = 100 \times \frac{OD_{\text{treated killed tissues}} - OD_{\text{non-treated killed tissues}}}{OD_{\text{negative control living tissues}}}$$

The NSMTT control per exposure time will be performed concurrently to the testing of the coloured test item.
If the NSMTT ≤ 5% only blank subtraction will be carried out.
If 5% < NSMTT ≤ 50% blank and appropriate background subtraction will be carried out.
If NSMTT > 50% results should be taken with caution.

For colouring test items, Non Specific Colour (NSC_{living}) relative to the Negative Control will be evaluated as follows:

$$NSC_{living} = 100 \times \frac{OD_{\text{test item (not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

The NSC_{living} control per exposure time will be performed concurrently to the testing of the coloured test item and in case of multiple testing, an independent NSC control will be conducted with each test performed (in each run).
If the $NSC_{living} \leq 5\%$ only blank subtraction will be carried out.
If $5\% < NSC_{living} \leq 50\%$ blank and appropriate background subtraction will be carried out.
If $NSC_{living} > 50\%$ results should be taken with caution.

For test items able both to stain tissue and reduce MTT, to avoid a possible double correction for colour interference, a third control for Non Specific Colour in killed tissues (NSC_{killed}) will be evaluated per exposure time:

$$NSC_{killed} = 100 \times \frac{OD_{\text{test item (treated killed tissues not incubated with MTT)}}}{OD_{\text{negative control living tissues}}}$$

If the $[(NSMTT + NSC_{living}) - NSC_{killed}] \leq 5\%$ this value will not be considered for the final calculation.
If $5\% < [(NSMTT + NSC_{living}) - NSC_{killed}] \leq 50\%$ blank subtraction and appropriate background subtraction will be carried out.
If $[(NSMTT + NSC_{living}) - NSC_{killed}] > 50\%$ results should be taken with caution.

A single NSC_{killed} control is sufficient per test item regardless of the number of independent tests/runs performed, but should be performed concurrently to the NSMTT control.

The above corrections should be applied when the mean OD value of test item treated tissues without any correction is within the linearity range of the spectrophotometer. In case of strong interference (OD values out of the linear range) the test item is not suitable for this test method.

7. REPORTING

7.1 Presentation of data

The results will be presented in the form of tables.

7.2 Interim Report

Any unexpected findings during the course of the study will be reported to the Sponsor's Monitoring Scientist immediately.

7.3 Final Report

A Draft Report will be sent to the Sponsor together with the Draft Report Approval Form. With the exception of signatures, the Draft Report will contain all information and data included in the Final Report.
Comments made by the Sponsor may be incorporated and the Final Report will be issued. If comments are not received within 6 months from despatch of the Draft Report, the Final Report will be issued.
The Final Report will include the information and data required by current internationally recognised regulations. The Final Report, digitally signed or with handwritten signatures, will be issued as PDF file, searchable, bookmarked and hyperlinked, fully compliant with the standard PDF/A-1b (ISO 19005-1 Level B), suitable for long term archiving of electronic document.

7.4 Corrections or additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the Final Report will be in the form of an amendment by the Study Director.

8. RECORDS AND ARCHIVES

Full records will be maintained of all aspects of study conduct, together with results of all measurements and observations. Prior to final archiving of the study data, a full list will be prepared of all records associated with the study.
A reserve sample of each batch of the test item will be taken and kept under the storage conditions of the bulk supply at ERBC. The reserve sample(s) of the test item will be retained within ERBC archives for a period of 10 years and then destroyed.
Any biological samples obtained for analytical measurements or similar determinations will be managed as indicated by the Sponsor in the Draft Report Approval Form or otherwise destroyed at no charge within 3 months from the issue of the Final Report.

The Final Protocol, the Final Report and electronic raw data generated by ERBC main validated systems (Pristima, Analyst, Empower, where used) will be archived at ERBC.

All other specimens, raw data, records and documentation generated during the course of this study will be archived at ERBC for a period of 3 years, after which the Sponsor will be contacted for shipment or disposal of the material (expenses will be charged to the Sponsor).

9. STUDY CONDUCT

9.1 Language

English and Italian renderings of chemical names, including that of the test material will be considered to be equivalent.

9.2 Scientific decisions

The procedures described in this Protocol may not comprehensively cover all the circumstances that can arise in the assay of the test items. When the study director considers it advisable to modify the procedures described for the selection of a solvent, interpretation of the outcome of the study or other aspects of the study conduct, he/she will carefully record the decision he/she has reached and the reasoning which led to it.

9.3 Quality assurance

According to the ERBC quality assurance programme, defined in the ERBC QA SOPs, this study will be subjected to the following procedures:

- the Protocol will be inspected,
- study/process based inspections of procedures/facilities will be carried out at intervals adequate to assure the integrity of the study,
- the Report will be inspected to assure that it accurately describes the methods and Standard Operating Procedures and that the results accurately reflect the raw data.

Periodic reports on these activities will be made to Management and Study Director.
All raw data pertaining to the study will be available for inspection by the Sponsor's Representative and Regulatory Authorities.

10. RESPONSIBILITIES OF THE SPONSOR

Items which are the responsibility of the Sponsor are indicated in section 2 of this Protocol. Since full compliance with regulatory requirements may depend on the performance of these items, the Sponsor should ensure that appropriate actions are initiated or undertaken.

11. REFERENCES

United Nations (UN) (2005). Globally Harmonised System of Classification and Labelling of Chemicals (GHS), First revised edition, UN New York and Geneva 2005.

ECVAM Protocol for EPISKIN™: an In Vitro Assay for Assessing Dermal Corrosivity Standard Operating Procedure (October 2000).

ICCVAM Evaluation of EPISKIN™, EpiDerm™ (EPI-200), and the Rat Skin Transcutaneous Electrical Resistance (TER) Assay: In Vitro test methods for Assessing Dermal Corrosivity Potential of Chemicals (NIH Publication No: 02-4502).

INVITTOX Protocol No. 118 EPISKIN™ Skin Corrosivity Test.

Version 20/1

PROTOCOL APPROVAL PAGE

for

ERBC S.r.l.

VERIFIED BY : _____ 01 Feb 2021
S. Cinelli, Biol.D., ERT — Date
Associate Scientific Director,
Head of Genetic Toxicology & Alternative Methods

APPROVED BY : _____ 01 Feb 2021
L. Bisini, Biol. D. — Date
Study Director

ERBC Study Number: A4248
ERBC Enquiry Number: O1788

February 2021

Version 20/1

PROTOCOL APPROVAL PAGE

for

Aughinish Alumina Ltd.

AUTHORISED BY : _____ 15/01/21
Date

Name and Title* : Senior Environmental Officer Rory O'Connor

* Please print or type your name and company status below your signature.

FINAL REPORT

Test Facility Study Code: 21/071-038CS

A GLP *In Vitro* Eye Irritation Test of Farmed Bauxite Residue in Isolated Chicken Eyes

SPONSOR:
Aughinish Alumina Ltd.
Aughinish Island,
Askeaton, Co. Limerick,
Ireland

TEST FACILITY:
Charles River Laboratories Hungary Kft.
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1.,
Hungary

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STATEMENT OF THE STUDY DIRECTOR

This study has been performed in accordance with the Study Plan agreed upon by Sponsor, the OECD Guidelines for Testing of Chemicals No. 438 (2018), Commission Regulation (EC) No 1272/2008 (2008), Commission Regulation (EC) 2017/735 of 2017 amending Regulation (EC) No 440/2008 (2008, B.48) and the Principles of Good Laboratory Practice as specified by national Hungarian GLP Regulations of 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study. By virtue of my dated signature I accept the responsibility for the validity of the data.

Signature: _____ Date: 23 July 2021

Balázs Orovecz, B.Sc.
Study Director

STATEMENT OF THE MANAGEMENT

According to the conditions of the research and development agreement between Aughinish Alumina Ltd. (as Sponsor) and Charles River Laboratories Hungary Kft. (as Test Facility), the study titled "A GLP *In Vitro* Eye Irritation Test of Farmed Bauxite Residue in Isolated Chicken Eyes" has been performed in compliance with Good Laboratory Practice.

Signature: Bala Tóth Date: 23 July 2021

Balázs Tóth, Ph.D.
General Manager

QUALITY ASSURANCE STATEMENT

Study Code: 21/071-038CS

Study Title: A GLP *In Vitro* Eye Irritation Test of Farmed Bauxite Residue in Isolated Chicken Eyes

Test Item: Farmed Bauxite Residue (Sample 1 Q2 2019, Sample 2 Q4 2019, Sample 3 Q1 2020 and Sample 4 Q4 2020)

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase (s) Inspected/Audited	Date of report to	
		Management	Study Director
17 May 2021	Study Plan	17 May 2021	17 May 2021
21 May 2021	Treatment	21 May 2021	21 May 2021
24 June 2021	Draft Report	24 June 2021	24 June 2021
05 July 2021	Amendment 1 to the Study Plan	05 July 2021	05 July 2021
21 July 2021	Final Report	21 July 2021	21 July 2021

Signature: Sebestyén Eszter

Date: 23 July 2021

Eszter Sebestyén, B.Sc.
On behalf of QA

1. SUMMARY

An *in vitro* eye irritation study of the four test items were performed in isolated chicken's eyes. The irritation effects of the test item were evaluated according to the OECD No. 438 guideline (25 June 2018).

In each experiment after the zero reference measurements, the eyes were held in a horizontal position and the test items were applied onto the centre of the cornea such that the entire surface of the cornea was covered in all cases. After 10 seconds exposure time, the surface of the eyes was rinsed with physiological saline solution. Three eyes were treated with 30 mg powdered test items in each experiment. The three positive control eyes were treated in a similar way with 30 mg powdered Imidazole and the negative control eye was treated with 30 µL of physiological saline (0.9% (w/v) NaCl solution in each experiment. Corneal thickness, corneal opacity and fluorescein retention were measured and any morphological effects (e.g. pitting or loosening of the epithelium) were evaluated.

Four experiment were performed in this study and two test items were used per experiments.

The results from all eyes used in the study met the quality control standards. The negative control and positive control results were within the historical control data range in experiments. Thus, the study was considered to be valid.

Sample 1 (Farmed Bauxite Residue - Sample 1 Q2 2019):

Experiment I: No significant corneal swelling change (mean = 3.2%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 1 on two eyes and severity 0.5 on one eye) was observed. Slight fluorescein retention change (severity 1 on two eyes and severity 0.5 on one eye) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Experiment III: No significant corneal swelling change (mean = 2.8%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 1 on two eyes and no corneal opacity change on one eye) was observed. No significant fluorescein retention change (severity 1 on one eye, severity 0.5 on one eye and no corneal opacity change on one eye) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Sample 2 (Farmed Bauxite Residue - Sample 2 Q4 2019):

Experiment I: No significant corneal swelling change (mean = 1.1%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 0.5 on two eyes and severity 1 on one eye) was observed. No significant fluorescein retention change (severity 0.5 on two eyes and no corneal opacity change on one eye) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Experiment III: No significant corneal swelling change (mean = 2.8%) was observed during the four-hour observation period on test item treated eyes. No significant corneal opacity change (severity 1 on one eye, severity 0.5 on one eye and no corneal opacity change on one eye) was observed. No significant fluorescein retention change (severity 0.5 on all three eyes) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Sample 3 (Farmed Bauxite Residue - Sample 3 Q1 2020):

Experiment II: No significant corneal swelling change (mean = 2.7%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 1 on all three eyes) was observed. Slight fluorescein retention change (severity 1 on all three eyes) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Experiment IV: No significant corneal swelling change (mean = 2.8%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 0.5 on two eyes and severity 1 on one eye) was observed. No significant fluorescein retention change (severity 0.5 on all three eyes) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Sample 4 (Farmed Bauxite Residue - Sample 4 Q4 2020):

Experiment II: No significant corneal swelling change (mean = 3.2%) was observed during the four-hour observation period on test item treated eyes. Slight corneal opacity change (severity 1 on all three eyes) was observed. No significant fluorescein retention change (severity 0.5 on two eyes and no corneal opacity change on one eye) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

Experiment IV: No significant corneal swelling change (mean = 1.1%) was observed during the four-hour observation period on test item treated eyes. No significant corneal opacity change (severity 0.5 on all three eye) was observed. No significant fluorescein retention change (severity 0.5 on two eyes and no fluorescein retention change on one eye) was noted. Minimal amount of test item (negligible) was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.

SUMMARY TABLE FOR UN GHS CLASSIFICATION
(all test item)

Criteria for "No category" (all true)	
3 endpoints classed as I or 2 endpoints classed as I and 1 endpoint classed as II or 1 endpoint classed as I and 2 endpoints classed as II:	True
No severe corneal morphological changes:	True
Test item was not stuck to the cornea at 240 minutes after the post-treatment rinse:	False*

Criteria for "Category 1" (one or more true)	
2 or more endpoints classed as IV:	False
Corneal opacity ≥ 3 at 30 min (in at least 2 eyes):	False
Corneal opacity = 4 at any time point (in at least 2 eyes):	False
Severe loosening of epithelium (in at least 1 eye):	False

Criteria for "No prediction can be made" (one or two true)	
Based on the endpoints not classifiable for No Category, or for Category 1:	False
Particles of test item were stuck to the cornea and could not be washed off during the study:	True*

Minimal amount of test item (negligible) was observed on the corneal surfaces all test item treated eyes in each experiment at 240 minutes after the post-treatment rinse. This fact had no impact classification of the test item. The cornea surfaces were considered clean.

Test item	Result of *In Vitro*				UN-GHS Classification
	Experiment I	Experiment II	Experiment III	Experiment IV	
Sample 1 Q2 2019	non-irritant	-	non-irritant	-	No Category
Sample 2 Q4 2019	non-irritant	-	non-irritant	-	No Category
Sample 3 Q1 2020	-	non-irritant	-	non-irritant	No Category
Sample 4 Q4 2020	-	non-irritant	-	non-irritant	No Category

Based on this *in vitro* eye irritation assay in isolated chicken eyes with Farmed Bauxite Residue (Sample 1 Q2 2019, Sample 2 Q4 2019, Sample 3 Q1 2020 and Sample 4 Q4 2020), the test items are non-irritant, UN-GHS Classification: No Category.

2. STUDY SCHEDULE

Study Plan: 18 May 2021

Amendment 1 to the Study Plan: 05 July 2021

Experimental Starting Date I: 21 May 2021

Experimental Completion Date I: 21 May 2021

Experimental Starting Date II: 25 May 2021

Experimental Completion Date II: 25 May 2021

Experimental Starting Date III: 07 June 2021

Experimental Completion Date III: 07 June 2021

Experimental Starting Date IV: 08 June 2021

Experimental Completion Date IV: 08 June 2021

Draft Report: 25 June 2021

Final Report: 23 July 2021

3. SPONSOR

Role	Name	Contact Information
Sponsor Representative / Study Monitor	Rory O'Dwyer	Address as cited for Sponsor Tel: + 0035361604074 E-mail: rory.odwyer@augh.com

4. RESPONSIBLE PERSONNEL

Role/Phase	Quality Assurance Unit (QAU	Name	Contact Information
Study Director	Charles River	Balázs Orovecz, B.Sc.	Address as cited for Test Facility Tel: +36 88 545 233 E-mail: balazs.orovecz@crl.com
Assistant Scientist	Charles River	Kata Tóth-Gönczöl, B.Sc.	Address as cited for Test Facility Tel: +36 88 545 265 E-mail: kata.toth-gonczol@crl.com
Test Facility Management	Charles River	Balázs Tóth, Ph.D., General Manager	Address as cited for Test Facility Tel: +36 88 545 200 E-mail: balazs.toth@crl.com
	Charles River	David J. Esdaile, M.Sc., Director of Science and Regulatory Affairs	Address as cited for Test Facility Tel: +36 88 545 200 E-mail: david.esdaile@crl.com
Test Facility QAU	Charles River	Eszter Sebestyén, B.Sc.	Address as cited for Test Facility Tel: +36 88 545 224 E-mail: eszter.sebestyen@crl.com
Other relevant personnel*			
Head of Pharmacy	Charles River	Tamás Mészáros, Ph.D.	Address as cited for Test Facility
Technical Team Leader	Charles River	Mihály Schmidt	Address as cited for Test Facility

*Note: Other trained, competent personnel worked on the study as required (as documented in the raw data).

5. OBJECTIVE

The Enucleated Eye Test with isolated eyes of chickens has been recognized as a valuable alternative to the Draize eye irritation test regarding ocular corrosivity or severe eye irritancy testing, because it represents a test system nearest to the *in vivo* test, without the need to use live animals. In the Isolated Chicken Eye Test (ICET) the test compound is applied in a single dose onto the cornea of isolated eyes, which are obtained from slaughter animals.

This method can provide detailed information about the effects of test items on the cornea, and can be used to identify chemicals not requiring classification for eye irritation, or for serious eye damage, as defined by the UN GHS (UN GHS non-classified or UN GHS Category 1). The test is described in OECD No. 438 and is approved by international regulatory agencies as a replacement for the identification of non-irritant, corrosives/severe irritants in the *in vivo* Rabbit Eye Assay (OECD No. 405).

6. GUIDELINES

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

OECD Guidelines for the Testing of Chemicals No. 438 (25 June 2018)

7. TEST MATERIALS

7.1. Test Items Characterization

The test items of a suitable chemical purity were supplied by the Sponsor. All precautions required in the handling and disposal of the test items were outlined by the Sponsor. These documents are part of the raw data. Test item was identified on the basis of the information provided by the Sponsor by the Pharmacy of Charles River Laboratories Hungary Kft. Copy of the Test Item data Sheet is shown in Appendix 1.

7.2. Test Items Identification

Information provided by the Sponsor:

Sample 1:

Name:	Farmed Bauxite Residue
Batch/Lot number:	Sample 1 Q2 2019
Description:	Red/brown solid
Purity:	Considered as 100% (70-75% solids)
Manufacturer/supplier:	Aughinish Alumina Ltd.
Expiry date:	03 February 2022

Sample 2:

Name:	Farmed Bauxite Residue
Batch/Lot number:	Sample 2 Q4 2019
Description:	Red/brown solid
Purity:	Considered as 100% (70-75% solids)
Manufacturer/supplier:	Aughinish Alumina Ltd.
Expiry date:	03 February 2022

Sample 3:

Name:	Farmed Bauxite Residue
Batch/Lot number:	Sample 3 Q1 2020
Description:	Red/brown solid
Purity:	Considered as 100% (70-75% solids)
Manufacturer/supplier:	Aughinish Alumina Ltd.
Expiry date:	03 February 2022

Sample 4:

Name:	Farmed Bauxite Residue
Batch/Lot number:	Sample 4 Q4 2020
Description:	Red/brown solid
Purity:	Considered as 100% (70-75% solids)
Manufacturer/supplier:	Aughinish Alumina Ltd.
Expiry date:	03 February 2022

7.3. Stability of Bulk Test Item

The test items are considered stable when stored under appropriate storage conditions: controlled room temperature (15-25°C, ≤70% relative humidity). The test items are stored in the Pharmacy of the Test Facility.

7.4. Negative Control Item Identification

Name:	Physiological saline (Salsol solution, 0.9% (w/v) NaCl)
Lot number:	203458142 / 210668141*
Manufacturer:	B. Braun Pharmaceuticals SA
Expiry Date:	31 July 2023 / 31 January 2024
Storage condition:	Room temperature

* Note: this batch was usen in Experiment III and IV.

7.5. Positive Control Item Identification

Name:	Imidazole
CAS Number:	288-32-4
Batch number:	A0410513
Expiry date:	31 July 2021
Manufacturer:	Acros Organics
Storage condition:	Room temperature

7.6. Reserve Samples

For each batch (lot) of test items and positive control items, a reserve sample (as specified in the relevant SOP) was collected and maintained under the appropriate storage conditions in the Archives of the Test Facility.

7.7. Test Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of test materials (including empty containers of Sponsor-provided materials) are maintained. All unused Sponsor-supplied bulk test materials, with the exception of reserve samples, will be returned to the Sponsor following issuance of the Draft Report.

7.8. Safety

Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to ensure personnel health and safety.

8. ADDITIONAL MATERIALS

8.1. Fluorescein retention test

Name:	Fluorescein, 10% (w/v) solution
Lot number:	320687F
Manufacturer:	Alcon
Expiry date:	31 October 2021
Storage condition:	Room temperature

This material was mixed with physiological saline Manufacturer: B. Braun Pharmaceuticals SA, Lot number: 94922Y05-1, Expiry date: 30 November 2022) to achieve the final concentration of 2% (w/v). The final solution was stored at room temperature (Dispensary code: S43218, Expiry date: 14 June 2021 in Experiment I-II and Dispensary code: S43220, Expiry date: 03 July 2021 in Experiment III-IV).

9. DOSE FORMULATION AND ANALYSIS

9.1. Preparation of Formulation

The test items were applied in its original form (although they were grounded to fine powder).

9.2. Sample Collection and Analysis

As there was no formulation step in the study, no analysis of the formulations for homogeneity and/or test item concentration was performed.

10. TEST SYSTEM

Strain of chicken:	ROSS 308 (in each experiment)
Source:	TARAVIS KFT. (Address: H-9600 Sárvár, Rábasömjéni utca 129., Hungary)

Chicken heads were collected after slaughter in a commercial abattoir from chickens (approximately 7 weeks old, mean weight: 2.5 kg in each experiment) which are used for human consumption. Heads were collected by a slaughter house technician and heads transported to Charles River Laboratories Hungary Kft. at ambient temperature at the earliest convenience.

After collection, the heads were inspected for appropriate quality and wrapped with tissue paper moistened with saline, then placed in a plastic box which was closed (4-5 heads per box). The heads were received at Charles River Laboratories Hungary Kft. and processed within 2 hours of collection in experiment.

10.1. Eyes selection

After removing the head from the plastic box, it was put on soft paper. The eyelids were carefully cut away with scissors, avoiding damaging the cornea. One small drop of 2% (w/v) fluorescein solution was applied onto the cornea surface for a few seconds and subsequently rinsed off with 20 mL physiological saline. Then the fluorescein-treated cornea was examined with a hand-held slit lamp or slit lamp microscope, with the eye in the head, to ensure that the cornea was not damaged (i.e. fluorescein retention and corneal opacity scores ≤ 0.5). If the cornea was in good condition, the eyeball was carefully removed from the orbit.

10.2. Preparation of eyes and Identification

The eyeball was carefully removed from the orbit by holding the nictitating membrane with a surgical forceps, while cutting the eye muscles with bent scissors. Care was taken to remove the eyeball from the orbit without cutting off the optical nerve too short. The procedure avoided pressure on the eye while removing the eyeball from the orbit, in order to prevent distortion of the cornea and subsequent corneal opacity. Once removed from the orbit, the eye was placed onto damp paper and the nictitating membrane was cut away with other connective tissue. The prepared eyes were kept on the wet papers in a closed box so that the appropriate humidity was maintained.

Each eye was located in chamber identified by a unique number within the Test Facility.

10.3. Eyes examination and acclimatization time

The prepared eye was placed in a steel clamp with the cornea positioned vertically with the eye in the correct relative position (same position as in the chicken head). Again avoid too much pressure on the eye by the clamp. Because of the relatively firm sclera of the chicken eyeball, only slight pressure was needed to fix the eye properly. The clamp with the eyeball was transferred to a chamber of the superfusion apparatus. The clamp holding the eye was positioned in such a way that the entire cornea was supplied with physiological saline solution dripping from a stainless steel tube, at a rate of approximately 3-4 drops/minute or 0.1 to 0.15 mL/minutes. The door of the chamber was closed except for manipulations and examinations, to maintain temperature and humidity.

The appropriate number of eyes was selected after being placed in the superfusion apparatus. There they were examined again with the slit lamp microscope to ensure that they were in good condition. The focus was adjusted to see clearly the physiological saline which was flowing on the cornea surface. Eyes with a high baseline fluorescein staining (*i.e.,* > 0.5) or corneal opacity score (*i.e.,* > 0.5) were rejected. The cornea thickness was measured, any eye with cornea thickness deviating more than 10 % from the mean value for all eyes, or eyes that showed any other signs of damage, were rejected and replaced. If the selected eyes were appropriate for the test, acclimatization started and it was conducted for approximately 45 to 60 minutes. The chambers of the superfusion apparatus were at controlled temperature (32±1.5°C) during the acclimatization and treatment periods.

11. TEST PROCEDURE

11.1. Solubility checking

The solubility of the test items in physiological saline was tested prior to the experiment (30 mg test material in 1 mL physiological saline (Manufacturer: B. Braun Pharmaceuticals SA, Lot number: 94922Y05-1, Expiry date: 30 November 2022). The test items dissolved in physiological saline.

11.2. Baseline assessments

At the end of the acclimatization period, a zero reference measurement was recorded for cornea thickness and opacity to serve as a baseline (t=0) for each individual eye. The cornea thickness of the eyes should not change by more than 5% within the -45 min and the zero time. No significant corneal thickness changes (1.7% was observed in four eyes and 1.8% in one eye in Experiment III), no corneal thickness changes were observed in the other eyes. Following the equilibration period, the fluorescein retention was measured. Baseline values were required to evaluate any potential test item related effect after treatment. All eyes were considered to be suitable for the assay.

11.3. Administration of Test and Control Items

After the zero reference measurements, the eye in its retainer was taken out of the chamber and placed on a layer of tissue with the cornea facing upwards. The eye was held in horizontal position, while the test material was applied onto the centre of the cornea.

30 mg of the powdered test items were applied onto the entire surface of the cornea attempting to cover the cornea surface uniformly with the test item, taking care not to damage or touch the cornea in experiments.

In each experiment, the positive control eyes were treated in a similar way with 30 mg powdered Imidazole. The negative control eye was treated with 30 µL of physiological saline (0.9% (w/v) NaCl solution).

Three test item treated eyes per test item, three positive control treated eyes and one negative control eye were examined during the study.

Group	Exposure			Number of eyes
	Volume	Duration	Rinsing	-
Experiment I				
Negative Control	30 µL	10 seconds	20 mL saline	1
Positive Control	30 mg	10 seconds	20 mL saline	3
Sample 1 Q2 2019	30 mg	10 seconds	20 mL saline	3
Sample 2 Q4 2019	30 mg	10 seconds	20 mL saline	3
Experiment II				
Negative Control	30 µL	10 seconds	20 mL saline	1
Positive Control	30 mg	10 seconds	20 mL saline	3
Sample 3 Q1 2020	30 mg	10 seconds	20 mL saline	3
Sample 4 Q4 2020	30 mg	10 seconds	20 mL saline	3
Experiment III				
Negative Control	30 µL	10 seconds	20 mL saline	1
Positive Control	30 mg	10 seconds	20 mL saline	3
Sample 1 Q2 2019	30 mg	10 seconds	20 mL saline	3
Sample 2 Q4 2019	30 mg	10 seconds	20 mL saline	3
Experiment IV				
Negative Control	30 µL	10 seconds	20 mL saline	1
Positive Control	30 mg	10 seconds	20 mL saline	3
Sample 3 Q1 2020	30 mg	10 seconds	20 mL saline	3
Sample 4 Q4 2020	30 mg	10 seconds	20 mL saline	3

11.4. Rinsing

The time of application was noted, then after an exposure period of 10 seconds from the end of the application the cornea surface was rinsed thoroughly with 20 mL physiological saline solution at ambient temperature, taking care not to damage the cornea but attempting to remove all residual test material if possible.

Additional gentle rinsing with 3*20 mL saline was performed (rinsing method was used with syringe) at additional time point when the test items and positive control material remaining on the cornea was observed.

Note: Physiological saline (Manufacturer: B. Braun Pharmaceuticals SA, Lot number: 203458143, Expiry date: 31 July 2023 in Experiment I-II and Lot number: 210668141, Expiry date: 31 January 2024 in Experiment III-IV) was used for rinsing.

11.5. Measurements

The negative and positive control eyes and all test item treated eyes were evaluated pre-treatment (as described in Section 11.2. Baseline assessments) and at approximately 30, 75, 120, 180 and 240 minutes after the post-treatment rinse. Minor variations within approximately ±5 minutes were considered acceptable. Haag-Streit BP 900® slit lamp microscope was used for the measurements.

Corneal thickness and corneal opacity were measured at each time point indicated above. Fluorescein retention was measured on two occasions, at base line (t=0) and approximately 30 minutes after the post-treatment rinse.

11.5.1. Corneal thickness determination

For thickness measurements, the slit lamp microscope was focused such that the physiological saline solution appeared as a visible, clear (sharp) image as it moved across the cornea surface.

11.5.2. Corneal opacity determination

For opacity determination, the slit lamp microscope was focused such that the physiological saline solution appeared as a visible, clear (sharp) image as it moved across the cornea surface.

11.5.3. Fluorescein retention determination

The fluorescein retention determination the settings of the slit lamp microscope was the same as for opacity assessment, but the green light filter was used.

11.6. Morphological effect

In each experiment minimal amount of test items were stuck on all cornea surfaces at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

The positive control material was stuck on all cornea surfaces after the post-treatment rinse, the cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.

No other morphological effect was observed in the study.

12. HISTOPATHOLOGY AND MICROSCOPIC EVALUATION

12.1. Sample collection

At the end of the procedure, the corneas were carefully removed from the eyes and placed individually into labelled containers of preservative fluid (10% neutral buffered formalin, Manufacturer: Lach-ner, Batch number: PP/2020/07895, Expiry date: 11 August 2021). The corneas are available for potential histopathology, stored at room temperature.

13. EVALUATION OF RESULT

13.1. Determination of corneal swelling

Corneal swelling is determined from corneal thickness measurements made with an optical pachymeter on a slit lamp microscope. It is expressed as a percentage and is calculated from corneal thickness measurements according to the following formulae:

$$CS \text{ at time } t = \frac{CT \text{ at time } t - CT \text{ at } t=0}{CT \text{ at } t=0} \times 100$$

$$\text{Mean } CS \text{ at time } t = \frac{FECS_{(\text{at time } t)} + SECS_{(\text{at time } t)} + TECS_{(\text{at time } t)}}{3}$$

where:
CS = corneal swelling
CT = cornea thickness
$FECS_{(at\ time\ t)}$ = corneal swelling of the first eye at a given time-point
$SECS_{(at\ time\ t)}$ = corneal swelling of the second eye at a given time-point
$TECS_{(at\ time\ t)}$ = cornea swelling of the third eye at a given time-point

For the calculation of maximum corneal swelling, small negative numbers for swelling following application (0 to -5%) are counted as zero (scored as class I). Large negative numbers (>12% below control) are probably due to erosion and indicate a severe effect (scored as class

IV). Cases of values of -5% to -12% are evaluated on a case by case basis but in the absence of other findings do not indicate a severe effect (class II).

13.2. Determination of opacity change

Corneal opacity is scored using the area of the cornea that is most densely opacified. The mean maximum cornea opacity change was calculated according to the following formulae:

$$\Delta CO \text{ at time } t = CO \text{ at time } t - CO \text{ at } t=0$$

$$\text{Mean } \Delta CO_{max} = \frac{FECO_{max(30min \text{ to } 240min)} + SECO_{max(30min \text{ to } 240min)} + TECO_{max(30min \text{ to } 240min)}}{3}$$

where:
CO *at time t* = cornea opacity at (30, 75, 120, 180 and 240) minutes after the post-treatment rinse
CO *at t=0* = baseline cornea opacity
ΔCO *at time t* = difference between cornea opacity at t time and the baseline value
FECO = cornea opacity of the first eye
SECO = cornea opacity of the second eye
TECO= cornea opacity of the third eye
$_{max(30min \text{ to } 240min)}$ = maximum opacity of the individual eye at 30 to 240 minutes minus baseline cornea opacity of the individual eye

13.3. Determination of fluorescein retention change

Fluorescein retention was calculated according to the following formulae:

$$\Delta FR \text{ at time } t = FR \text{ at time } t - FR \text{ at } t=0$$

$$\text{Mean } \Delta FR = \frac{FEFR_{(30min)} + SEFR_{(30min)} + TEFR_{(30min)}}{3}$$

where:
FR *at time t* = fluorescein retention at 30 minutes after the post-treatment rinse
FR *at t=0* = baseline fluorescein retention
ΔFR *at time t* = difference between fluorescein retention at t time and the baseline value
FEFR = first eye fluorescein retention at 30 minutes after the post-treatment rinse minus the baseline value
SEFR = second eye fluorescein retention at 30 minutes after the post-treatment rinse minus the baseline value
TEFR = third eye fluorescein retention at 30 minutes after the post-treatment rinse minus the baseline value

14. ARCHIVES

The study documents and samples:

- study plan and amendment,
- all raw data,
- sample of the test items and positive controls,
- study report and any amendments,
- correspondence,
- corneas

will be stored in the Archives of Charles River Laboratories Hungary Kft. (H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary) according to the Hungarian GLP [5] and to Charles River Laboratories Hungary Kft. SOPs for 15 years.

After the retention time has elapsed, all the archived materials listed above would be offered to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded (with the exception of the original Study Plan and any amendment(s), and the

original Final Report and any amendment(s), which will be kept in the Archive of the Test Facility or transferred to external archiving).

15. COMPUTERIZED SYSTEMS

The following computerized systems were used in the study.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis v9.3	test item receipt

16. RESULTS

The mean values of the treated eyes for maximum corneal thickness change, corneal opacity change and fluorescein retention change are given below. The conclusion on eye irritancy was based on the relevant OECD guideline quantitative assessments, shown in Appendix 3 and 4.

Details of data interpretation for Isolated Chicken Eye (ICE) Class under OECD classification are given in Appendix 3 and 4. The mean maximum corneal swelling up to 240 min, the mean maximum corneal opacity change and the mean fluorescein retention change ICE classes are used GHS classification.

16.1. Test Items

Sample 1 Q2 2019:

Experiment I		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	3.2%	I
Mean maximum corneal swelling at up to 240 min	3.2%	I
Mean maximum corneal opacity change	0.83	II
Mean fluorescein retention change	0.83	II
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	1xI 2xII	

Experiment III		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	2.8%	I
Mean maximum corneal swelling at up to 240 min	2.8%	I
Mean maximum corneal opacity change	0.67	II
Mean fluorescein retention change	0.50	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	2xI 1xII	

The test item Sample 1 Q2 2019 showed no corneal effect in the first experiment. As the test item was solid, the negative results were confirmed by a second experiment according to the recommendations of the OECD No. 438 guideline. The second experiment confirmed the negative results. Therefore, based on these *in vitro* eye irritation tests in isolated chicken eyes with Sample 1 Q2 2019, the test item is non-irritant. UN-GHS Classification: No Category.

Sample 2 Q4 2019:

Experiment I		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	1.1%	I
Mean maximum corneal swelling at up to 240 min	1.1%	I
Mean maximum corneal opacity change	0.67	II
Mean fluorescein retention change	0.33	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	2xI 1xII	

Experiment III		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	2.2%	I
Mean maximum corneal swelling at up to 240 min	2.8%	I
Mean maximum corneal opacity change	0.50	I
Mean fluorescein retention change	0.50	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	3xI	

The test item Sample 2 Q4 2019 showed no corneal effect in the first experiment. As the test item was solid, the negative results were confirmed by a second experiment according to the recommendations of the OECD No. 438 guideline. The second experiment confirmed the negative results. Therefore, based on these *in vitro* eye irritation tests in isolated chicken eyes with Sample 2 Q4 2019, the test item is non-irritant. UN-GHS Classification: No Category.

Sample 3 Q1 2020:

Experiment II		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	1.1%	I
Mean maximum corneal swelling at up to 240 min	2.7%	I
Mean maximum corneal opacity change	1.00	II
Mean fluorescein retention change	1.00	II
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse..	
Overall ICE Class	1xI 2xII	

Experiment IV		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	2.8%	I
Mean maximum corneal swelling at up to 240 min	2.8%	I
Mean maximum corneal opacity change	0.67	II
Mean fluorescein retention change	0.50	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	2xI 1xII	

The test item Sample 3 Q1 2020 showed no corneal effect in the first experiment. As the test item was solid, the negative results were confirmed by a second experiment according to the recommendations of the OECD No. 438 guideline. The second experiment confirmed the negative results. Therefore, based on these *in vitro* eye irritation tests in isolated chicken eyes with Sample 3 Q1 2020, the test item is non-irritant. UN-GHS Classification: No Category.

Sample 4 Q4 2020:

Experiment II		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	0.0%	I
Mean maximum corneal swelling at up to 240 min	3.2%	I
Mean maximum corneal opacity change	1.00	II
Mean fluorescein retention change	0.33	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	2xI 1xII	

Experiment IV		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	0.6%	I
Mean maximum corneal swelling at up to 240 min	1.1%	I
Mean maximum corneal opacity change	0.50	I
Mean fluorescein retention change	0.33	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces at 240 minutes after the post-treatment rinse.	
Overall ICE Class	3xI	

The test item Sample 4 Q4 2020 showed no corneal effect in the first experiment. As the test item was solid, the negative results were confirmed by a second experiment according to the recommendations of the OECD No. 438 guideline. The second experiment confirmed the negative results. Therefore, based on these *in vitro* eye irritation tests in isolated chicken eyes with Sample 4 Q4 2020, the test item is non-irritant. UN-GHS Classification: No Category.

16.2. Positive Control

Experiment I		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	13.0%	III
Mean maximum corneal swelling at up to 240 min	23.8%	III
Mean maximum corneal opacity change	3.83	IV
Mean fluorescein retention change	2.83	IV
Other Observations	Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.	
Overall ICE Class	1xIII 2xIV	

Experiment II		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	10.3%	II
Mean maximum corneal swelling at up to 240 min	22.3%	III
Mean maximum corneal opacity change	4.00	IV
Mean fluorescein retention change	2.83	IV
Other Observations	Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.	
Overall ICE Class	1xIII 2xIV	

Experiment III		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	11.8%	II
Mean maximum corneal swelling at up to 240 min	26.4%	III
Mean maximum corneal opacity change	3.83	IV
Mean fluorescein retention change	2.83	IV
Other Observations	Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.	
Overall ICE Class	1xIII 2xIV	

Experiment IV		
Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	9.8%	II
Mean maximum corneal swelling at up to 240 min	20.5%	III
Mean maximum corneal opacity change	3.83	IV
Mean fluorescein retention change	2.83	IV
Other Observations	Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.	
Overall ICE Class	1xIII 2xIV	

Based on these observations, the positive control substance Imidazole was classified as severe irritant according to the EU regulations in each experiment. UN GHS Classification: Category 1.

16.3. Negative Control

Experiment I		
Observation	Value	ICE Class
Maximum corneal swelling at up to 75 min	0.0%	I
Maximum corneal swelling at up to 240 min	0.0%	I
Maximum corneal opacity change	0.00	I
Fluorescein retention change	0.50	I
Other Observations	None	
Overall ICE Class	3xI	

Experiment II		
Observation	Value	ICE Class
Maximum corneal swelling at up to 75 min	0.0%	I
Maximum corneal swelling at up to 240 min	0.0%	I
Maximum corneal opacity change	0.00	I
Fluorescein retention change	0.00	I
Other Observations	None	
Overall ICE Class	3xI	

Experiment III		
Observation	Value	ICE Class
Maximum corneal swelling at up to 75 min	0.0%	I
Maximum corneal swelling at up to 240 min	0.0%	I
Maximum corneal opacity change	0.00	I
Fluorescein retention change	0.50	I
Other Observations	None	
Overall ICE Class	3xI	

Experiment IV		
Observation	Value	ICE Class
Maximum corneal swelling at up to 75 min	0.0%	I
Maximum corneal swelling at up to 240 min	1.6%	I
Maximum corneal opacity change	0.00	I
Fluorescein retention change	0.00	I
Other Observations	None	
Overall ICE Class	3xI	

The negative control Physiological saline was classified as non-irritating in each experiment. UN GHS Classification: No Category.

17. VALIDITY CRITERIA

The results from all eyes used met the quality control standards. The negative control and positive control results were within the historical control data range. This study was considered to be valid.

18. DEVIATIONS TO THE STUDY PLAN

There were no deviations to the Study Plan.

19. CONCLUSION

SUMMARY TABLE FOR UN GHS CLASSIFICATION
(all test item)

Criteria for "No category" (all true)	
3 endpoints classed as I or 2 endpoints classed as I and 1 endpoint classed as II or 1 endpoint classed as I and 2 endpoints classed as II:	True
No severe corneal morphological changes:	True
Test item was not stuck to the cornea at 240 minutes after the post-treatment rinse:	False*

Criteria for "Category 1" (one or more true)	
2 or more endpoints classed as IV:	False
Corneal opacity ≥ 3 at 30 min (in at least 2 eyes):	False
Corneal opacity = 4 at any time point (in at least 2 eyes):	False
Severe loosening of epithelium (in at least 1 eye):	False

Criteria for "No prediction can be made" (one or two true)	
Based on the endpoints not classifiable for No Category, or for Category 1:	False
Particles of test item were stuck to the cornea and could not be washed off during the study:	True*

* Minimal amount of test item (negligible) was observed on the corneal surfaces all test item treated eyes in each experiment at 240 minutes after the post-treatment rinse. This fact had no impact classification of the test item. The cornea surfaces were considered clean.

Based on this *in vitro* eye irritation assay in isolated chicken eyes with Farmed Bauxite Residue (Sample 1 Q2 2019, Sample 2 Q4 2019, Sample 3 Q1 2020 and Sample 4 Q4 2020), the test items are non-irritant, UN-GHS Classification: No Category.

20. DISTRIBUTION OF THE FINAL REPORT

Sponsor: 1x PDF file

Archive: 1x original, bound

21. REFERENCES

1. OECD Guidelines for the Testing of Chemicals 438 (2018)
2. Commission Regulation (EU) 2017/735 of 14 February 2017 amending, for the purpose of its adaptation to technical progress, the Annex to Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
3. EU Commission Regulation (EC) No 1272/2008 (2008) on CLP
4. OECD No. 160: Guidance document on "the bovine corneal opacity and permeability (BCOP) and isolated chicken eye (ICE) test methods: Collection of tissues for histological evaluation and collection of data on non-severe irritants (2017)
5. Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.
6. United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Eighth revised edition, UN New York and Geneva (2019)
7. OECD Guidelines for Testing Chemicals, 405 (2017) MENK K. PRINSEN, M.E.I. SCHIPPER, M.V.W. WIJNANDS: Histopathology in the isolated chicken eye test and comparison of different stainings of the cornea. Toxicology in Vitro 25 (2011) 1475-1479

A P P E N D I C E S

APPENDIX 1

COPY OF THE TEST ITEM DATA SHEET

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TEST ITEM DATA SHEET

charles river

This questionnaire allows us to safely store, handle and properly administer your test substance. All data will be treated as strictly confidential. Please save the completed form in pdf and send it directly to the following email address: ves-testitem@crl.com. Please also send Certificate of Analysis (CoA) and Safety Data Sheet (SDS) if available.

1. SPONSOR (as defined by GLP)			
Company *	Aughinish Alumina	**Contact Person ***	Rory O'Dwyer
Address *	Aughinish Island Askeaton Co. Limerick	**Phone**	0035361604074
		Fax	
		E-mail *	rory.odwyer@augh.com

2. TEST ITEM INFORMATION				
Test item name * (As it should be used in report)	Bauxite residue			
Substance classification*	☐ Pharmaceutical	☒ Industrial Chemical	☐ Agrochemical	☐ Other
Chemical name (IUPAC, CAS if applicable)	--			
Other names, synonyms (if applicable)	Red Mud			
Batch (Lot) number *	Sample 1 Q2 2019 / Sample 2 Q4 2019 Sample 3 Q1 2020 / Sample 4 Q4 2020		☐ See CoA / Container	
Description * (Colour, Appearance at 20 °C)	Red/brown solid		☐ See CoA / SDS	
Expiry (Retest) date * (day-month-year)	N/A	☐ See CoA / Container	**If not indicated, 1 year from date of receipt is applied.**	
CAS number (if available)	N/A	**Molecular weight** (if applicable)	N/A	☐ Salt form
Molecular formula (if applicable, use TIDS Appendix to present structural formula)	N/A	**Quantity *** (Sent by Sponsor)	~10g per sample	☐ See label
Purity / Concentration * (Otherwise treated as 100%)	70-75 % solids		☐ See CoA / Container	
Storage conditions * Test item will be stored at **Room temperature (15-25°C, ≤ 70 RH%) **** unless specified otherwise (Test item storeroom is well ventilated and protected from direct sunlight.)	☐ Refrigerated (2-8°C)	☐ Frozen (≤ -15°C)	☐ Ultra-low (≤ -70°C)	
	☐ Protected from humidity (tight closed container)		☐ Protected from humidity (beside silica)	
	☐ Protected from light	☐ Under inert gas (e.g. N_2)	☐ See CoA / Container	
	☐ Other (than room temperature):			
Hazards information Please provide available SDS. If no SDS is available, please indicate known or suspected hazards	☐ Unknown	☐ Flammable	☐ Oxidising	☐ Corrosive
	☐ Irritant	☐ Oral toxicity	☐ Inhalation toxicity	☐ Teratogenic
	☐ Mutagenic	☐ Carcinogenic	☐ Hazardous to the aquatic environment	
	☒ Non-hazardous	☐ Other:		
Safety precautions (if no SDS is available)	See SDS sent with this document			

** = Mandatory fields* *** = Default storage condition (if no checkbox is marked, test item will be stored at room temperature)*

APPENDIX 1

COPY OF THE TEST ITEM DATA SHEET
(continued)

CONFIDENTIAL **Page: 2 / 2**

3. PHYSICAL-CHEMICAL PARAMETERS AND SOLUBILITY INFORMATION				
pH (at g/L at °C)	~pH 11	**Density (g/cm³ at °C)**	See SDS	☐ See CoA / SDS
Other known parameters (e.g. melting point, boiling point, vapour pressure, viscosity, etc.)	See SDS			
Solution / suspension preparation The following may be used as vehicles, solvents or suspending agents. Please indicate suitability	☒ Water ☐ Saline ☐ 1% Aq. Methylcellulose ☐ Ethanol ☐ Methanol ☐ Propylene glycol ☐ Polyethylene glycol ☐ Methyl ethyl ketone ☐ Corn oil ☐ Olive oil ☐ Acetone ☐ Acetonitrile ☐ Dimethyl sulfoxide ☐ *N,N*-Dimethylformamide ☐ Other:			
Preferred vehicle(s) and known stability data (concentration, temperature, duration, pH value, light conditions, osmolality etc.)	See SDS			
Analytical method for quantitative analysis	☐ Not available ☐ Available and attached ☐ Can be provided upon request			

4. FORMULATION, SAMPLE PREPARATION AND OTHER INSTRUCTIONS			
Test item can be heated	☒ Yes (up to 120°C) ☐ No	**Grinding in a mortar or in a mill is acceptable**	☒ Yes ☐ Not applicable
Dose formulation or solution can be heated	☒ Yes (up to 120°C) ☐ No	**Sonication can be used to aid dissolution**	☒ Yes ☐ Not applicable
Preferable materials for test item or formulation containers	☐ Glass ☒ Plastic, type: ☐ Other: ☐ Special pre-treatment or cleaning procedure is necessary (please give instructions below)		
Special preparation or handling requirements and instructions	N/A		
Incompatible or may interfere with material(s)	Will react with acid – mild reaction		

5. TEST ITEM SHIPMENT (If no information is provided, test item can be shipped as a normal package)	
Shipment conditions	☒ Normal package ☐ Icepacks ☐ Dry ice ☐ Other:
Shipping restrictions (if no SDS is available)	

6. DISPOSAL (If no information provided, test item will be disposed after finalisation of all studies)	
Remaining Test item *	☐ Dispose ☒ Return ☐ Specified at General remarks

- Unless required otherwise, test item will be disposed in a safe and proper manner after finalization of all studies or 3 months after sending the (draft) reports.
- In accordance with GLP regulations Charles River Laboratories Hungary Kft. reserves the right to retain a reference sample per each test item for archiving.
- Returning test item will be at the expense of the Sponsor. If additional charges are applicable the Sponsor's agreement will be obtained prior to dispatch.

General remarks			
On behalf of Sponsor ** (Signed or electronically sent by)	Rory O'Dwyer	**Date *** (day-month-year)	01 February 2021

** = Mandatory fields* *** = If TIDS sent in pdf, typed name is sufficient, if sent only in paper form, wet ink signature is necessary.*

Delivery Address:
Pharmacy Department
Charles River Laboratories Hungary Kft.
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1
HUNGARY
Tel: +36 88 545 300
Fax: +36 88 545 301
E-mail: ves-testitem@crl.com

Charles River Laboratories Hungary Kft. – TEST ITEM DATA SHEET

APPENDIX 2

TABLES OF INDIVIDUAL DATA

TABLE 1.1
Table of individual data Farmed Bauxite Residue (Sample 1 Q2 2019)
Experiment I

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	21 May 2021															Test Item:	Farmed Bauxite Residue (Sample 1 Q2 2019)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
1	62	62	0.0%	64	*3.2%*	64	*3.2%*	*3.2%*	64	*3.2%*	64	*3.2%*	64	*3.2%*	*3.2%*	0	1	1	1	1	1	*1.0*	0	1	*1.0*
2	60	60	0.0%	62	*3.3%*	62	*3.3%*	*3.3%*	62	*3.3%*	62	*3.3%*	62	*3.3%*	*3.3%*	0	1	1	1	1	1	*1.0*	0	1	*1.0*
3	63	63	0.0%	65	*3.2%*	65	*3.2%*	*3.2%*	65	*3.2%*	65	*3.2%*	65	*3.2%*	*3.2%*	0	0.5	0.5	0.5	0.5	0.5	*0.5*	0.5	1	*0.5*
Mean values:					*3.2%*		*3.2%*	*3.2%*		*3.2%*		*3.2%*		*3.2%*	*3.2%*							*0.83*			*0.83*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

TABLE 1.2
Table of individual data Farmed Bauxite Residue (Sample 1 Q2 2019)
Experiment III

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	07 June 2021															Test Item:	Farmed Bauxite Residue (Sample 1 Q2 2019)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
1	58	58	0.0%	60	*3.4%*	60	*3.4%*	*3.4%*	60	*3.4%*	60	*3.4%*	60	*3.4%*	*3.4%*	0	0.5	0.5	0.5	1	1	*1.0*	0	1	*1.0*
2	60	61	1.7%	62	*1.6%*	62	*1.6%*	*1.6%*	62	*1.6%*	62	*1.6%*	62	*1.6%*	*1.6%*	0.5	0.5	0.5	0.5	0.5	0.5	*0.0*	0	0.5	*0.5*
3	60	60	0.0%	62	*3.3%*	62	*3.3%*	*3.3%*	62	*3.3%*	62	*3.3%*	62	*3.3%*	*3.3%*	0	1	1	1	1	1	*1.0*	0.5	0.5	*0.0*
Mean values:					*2.8%*		*2.8%*	*2.8%*		*2.8%*		*2.8%*		*2.8%*	*2.8%*							*0.67*			*0.50*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.3
Table of individual data Farmed Bauxite Residue (Sample 2 Q4 2019)
Experiment I

Study Code:	21/071-038CS														Strain:	ROSS 308								
Date of Exposure:	21 May 2021														Test Item:	Farmed Bauxite Residue (Sample 2 Q4 2019)								
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
4	60	60	0.0%	60	*0.0%*	60	*0.0%*	*0.0%*	60	*0.0%*	60	*0.0%*	60	*0.0%*	*0.0%*	0	0	1	1	1	1	*1.0*	0	0	*0.0*
5	60	60	0.0%	61	*1.7%*	61	*1.7%*	*1.7%*	61	*1.7%*	61	*1.7%*	61	*1.7%*	*1.7%*	0	0	0.5	0.5	0.5	0.5	*0.5*	0	0.5	*0.5*
6	62	62	0.0%	63	*1.6%*	63	*1.6%*	*1.6%*	63	*1.6%*	63	*1.6%*	63	*1.6%*	*1.6%*	0	0	0.5	0.5	0.5	0.5	*0.5*	0.5	1	*0.5*
Mean values:					*1.1%*		*1.1%*	*1.1%*		*1.1%*		*1.1%*		*1.1%*	*1.1%*							*0.67*			*0.33*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

TABLE 1.4
Table of individual data Farmed Bauxite Residue (Sample 2 Q4 2019)
Experiment III

Study Code:	21/071-038CS														Strain:	ROSS 308								
Date of Exposure:	07 June 2021														Test Item:	Farmed Bauxite Residue (Sample 2 Q4 2019)								
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
4	60	60	0.0%	62	*3.3%*	62	*3.3%*	*3.3%*	62	*3.3%*	62	*3.3%*	62	*3.3%*	*3.3%*	0	0.5	0.5	1	1	1	*1.0*	0	0.5	*0.5*
5	59	60	1.7%	61	*1.7%*	61	*1.7%*	*1.7%*	61	*1.7%*	62	*3.3%*	62	*3.3%*	*3.3%*	0	0.5	0.5	0.5	0.5	0.5	*0.5*	0.5	1	*0.5*
6	60	61	1.7%	62	*1.6%*	62	*1.6%*	*1.6%*	62	*1.6%*	62	*1.6%*	62	*1.6%*	*1.6%*	0.5	0.5	0.5	0.5	0.5	0.5	*0.0*	0	0.5	*0.5*
Mean values:					*2.2%*		*2.2%*	*2.2%*		*2.2%*		*2.8%*		*2.8%*	*2.8%*							*0.50*			*0.50*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.5
Table of individual data Farmed Bauxite Residue (Sample 3 Q1 2020)
Experiment II

Study Code:	21/071-038CS															Strain:	ROSS 308								
Date of Exposure:	25 May 2021															Test Item:	Farmed Bauxite Residue (Sample 3 Q1 2020)								
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
1	61	61	0.0%	61	*0.0%*	62	*1.6%*	*1.6%*	62	*1.6%*	62	*1.6%*	62	*1.6%*	*1.6%*	0	0	1	1	1	1	*1.0*	0	1	*1.0*
2	62	62	0.0%	63	*1.6%*	63	*1.6%*	*1.6%*	63	*1.6%*	63	*1.6%*	64	*3.2%*	*3.2%*	0	0.5	1	1	1	1	*1.0*	0	1	*1.0*
3	62	62	0.0%	62	*0.0%*	62	*0.0%*	*0.0%*	64	*3.2%*	64	*3.2%*	64	*3.2%*	*3.2%*	0	0.5	1	1	1	1	*1.0*	0	1	*1.0*
Mean values:					*0.5%*		*1.1%*	*1.1%*		*2.2%*		*2.2%*		*2.7%*	*2.7%*							*1.00*			*1.00*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

TABLE 1.6
Table of individual data Farmed Bauxite Residue (Sample 3 Q1 2020)
Experiment IV

Study Code:	21/071-038CS															Strain:	ROSS 308								
Date of Exposure:	08 June 2021															Test Item:	Farmed Bauxite Residue (Sample 3 Q1 2020)								
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
1	61	61	0.0%	63	*3.3%*	63	*3.3%*	*3.3%*	63	*3.3%*	63	*3.3%*	63	*3.3%*	*3.3%*	0.5	0.5	0.5	0.5	1	1	*0.5*	0	0.5	*0.5*
2	61	61	0.0%	62	*1.6%*	62	*1.6%*	*1.6%*	62	*1.6%*	62	*1.6%*	62	*1.6%*	*1.6%*	0	0.5	0.5	0.5	0.5	1	*1.0*	0	0.5	*0.5*
3	58	58	0.0%	60	*3.4%*	60	*3.4%*	*3.4%*	60	*3.4%*	60	*3.4%*	60	*3.4%*	*3.4%*	0	0	0	0.5	0.5	0.5	*0.5*	0	0.5	*0.5*
Mean values:					*2.8%*		*2.8%*	*2.8%*		*2.8%*		*2.8%*		*2.8%*	*2.8%*							*0.67*			*0.50*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.7
Table of individual data Farmed Bauxite Residue (Sample 4 Q4 2020)
Experiment II

Study Code:	21/071-038CS														Strain:	ROSS 308								
Date of Exposure:	25 May 2021														Test Item:	Farmed Bauxite Residue (Sample 4 Q4 2020)								
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
4	62	62	0.0%	62	*0.0%*	62	*0.0%*	*0.0%*	64	*3.2%*	64	*3.2%*	64	*3.2%*	*3.2%*	0	0	0.5	0.5	1	1	*1.0*	0	0.5	*0.5*
5	63	63	0.0%	63	*0.0%*	63	*0.0%*	*0.0%*	65	*3.2%*	65	*3.2%*	65	*3.2%*	*3.2%*	0	0	0.5	0.5	1	1	*1.0*	0	0.5	*0.5*
6	62	62	0.0%	62	*0.0%*	62	*0.0%*	*0.0%*	64	*3.2%*	64	*3.2%*	64	*3.2%*	*3.2%*	0	0.5	1	1	1	1	*1.0*	0.5	0.5	*0.0*
Mean values:					*0.0%*		*0.0%*	*0.0%*		*3.2%*		*3.2%*		*3.2%*	*3.2%*							*1.00*			*0.33*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

TABLE 1.8
Table of individual data Farmed Bauxite Residue (Sample 4 Q4 2020)
Experiment IV

Study Code:	21/071-038CS														Strain:	ROSS 308								
Date of Exposure:	08 June 2021														Test Item:	Farmed Bauxite Residue (Sample 4 Q4 2020)								
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score							Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
4	63	63	0.0%	63	*0.0%*	63	*0.0%*	*0.0%*	64	*1.6%*	64	*1.6%*	64	*1.6%*	*1.6%*	0.5	0.5	0.5	1	1	1	*0.5*	0	0.5	*0.5*
5	60	60	0.0%	61	*1.7%*	61	*1.7%*	*1.7%*	61	*1.7%*	61	*1.7%*	61	*1.7%*	*1.7%*	0	0	0	0.5	0.5	0.5	*0.5*	0	0.5	*0.5*
6	60	60	0.0%	60	*0.0%*	60	*0.0%*	*0.0%*	60	*0.0%*	60	*0.0%*	60	*0.0%*	*0.0%*	0	0	0	0	0.5	0.5	*0.5*	0.5	0.5	*0.0*
Mean values:					*0.6%*		*0.6%*	*0.6%*		*1.1%*		*1.1%*		*1.1%*	*1.1%*							*0.50*			*0.33*

Note: Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.9
Table of individual data Imidazole
Experiment I

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	21 May 2021															Positive Control:	Imidazole									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
7	62	62	0.0%	68	*9.7%*	70	*12.9%*	*12.9%*	72	*16.1%*	74	*19.4%*	76	*22.6%*	*22.6%*	0.5	4	4	4	4	4	*3.5*	0.5	3	*2.5*
8	63	63	0.0%	66	*4.8%*	69	*9.5%*	*9.5%*	72	*14.3%*	75	*19.0%*	76	*20.6%*	*20.6%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
9	60	60	0.0%	67	*11.7%*	70	*16.7%*	*16.7%*	71	*18.3%*	74	*23.3%*	77	*28.3%*	*28.3%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
Mean values:					*8.7%*		*13.0%*	*13.0%*		*16.2%*		*20.6%*		*23.8%*	*23.8%*							*3.83*			*2.83*

Note: Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.

TABLE 1.10
Table of individual data Imidazole
Experiment II

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	25 May 2021															Positive Control:	Imidazole									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
7	62	62	0.0%	66	*6.5%*	69	*11.3%*	*11.3%*	72	*16.1%*	75	*21.0%*	76	*22.6%*	*22.6%*	0	4	4	4	4	4	*4.0*	0.5	3	*2.5*
8	60	60	0.0%	64	*6.7%*	67	*11.7%*	*11.7%*	70	*16.7%*	72	*20.0%*	74	*23.3%*	*23.3%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
9	62	62	0.0%	65	*4.8%*	67	*8.1%*	*8.1%*	71	*14.5%*	73	*17.7%*	75	*21.0%*	*21.0%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
Mean values:					*6.0%*		*10.3%*	*10.3%*		*15.8%*		*19.6%*		*22.3%*	*22.3%*							*4.00*			*2.83*

Note: Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.11
Table of individual data Imidazole
Experiment III

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	07 June 2021															Positive Control:	Imidazole									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
7	58	58	0.0%	62	*6.9%*	66	*13.8%*	*13.8%*	69	*19.0%*	73	*25.9%*	75	*29.3%*	*29.3%*	0	4	4	4	4	4	*4.0*	0.5	3	*2.5*
8	61	61	0.0%	64	*4.9%*	67	*9.8%*	*9.8%*	70	*14.8%*	74	*21.3%*	76	*24.6%*	*24.6%*	0.5	4	4	4	4	4	*3.5*	0	3	*3.0*
9	58	59	1.7%	63	*6.8%*	66	*11.9%*	*11.9%*	70	*18.6%*	72	*22.0%*	74	*25.4%*	*25.4%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
Mean values:					*6.2%*		*11.8%*	*11.8%*		*17.5%*		*23.1%*		*26.4%*	*26.4%*							*3.83*			*2.83*

Note: Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.

TABLE 1.12
Table of individual data Imidazole
Experiment IV

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	08 June 2021															Positive Control:	Imidazole									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
7	60	60	0.0%	68	*13.3%*	68	*13.3%*	*13.3%*	69	*15.0%*	70	*16.7%*	72	*20.0%*	*20.0%*	0	4	4	4	4	4	*4.0*	0.5	3	*2.5*
8	63	63	0.0%	67	*6.3%*	69	*9.5%*	*9.5%*	70	*11.1%*	73	*15.9%*	75	*19.0%*	*19.0%*	0.5	4	4	4	4	4	*3.5*	0	3	*3.0*
9	62	62	0.0%	64	*3.2%*	66	*6.5%*	*6.5%*	69	*11.3%*	70	*12.9%*	76	*22.6%*	*22.6%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
Mean values:					*7.6%*		*9.8%*	*9.8%*		*12.5%*		*15.1%*		*20.5%*	*20.5%*							*3.83*			*2.83*

Note: Imidazole was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces were not cleared at 240 minutes after the post-treatment rinse.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.14
Table of individual data Physiological saline
Experiment I

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	21 May 2021															Negative Control:	Physiological saline (NaCl 0.9% w/v)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
10	60	60	0.0%	60	*0.0%*	60	*0.0%*	*0.0%*	60	*0.0%*	60	*0.0%*	60	*0.0%*	*0.0%*	0	0	0	0	0	0	*0.00*	0	0.5	*0.50*

Note: No morphological effect was observed.

TABLE 1.15
Table of individual data Physiological saline
Experiment II

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	25 May 2021															Negative Control:	Physiological saline (NaCl 0.9% w/v)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
10	60	60	0.0%	60	*0.0%*	60	*0.0%*	*0.0%*	60	*0.0%*	60	*0.0%*	60	*0.0%*	*0.0%*	0	0	0	0	0	0	*0.00*	0	0	*0.00*

Note: No morphological effect was observed.

APPENDIX 2

TABLES OF INDIVIDUAL DATA
(Continued)

TABLE 1.16
Table of individual data Physiological saline
Experiment III

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	07 June 2021															Negative Control:	Physiological saline (NaCl 0.9% w/v)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
10	57	58	1.8%	58	*0.0%*	58	*0.0%*	*0.0%*	58	*0.0%*	58	*0.0%*	58	*0.0%*	*0.0%*	0	0	0	0	0	0	*0.00*	0	0.5	*0.50*

Note: No morphological effect was observed.

TABLE 1.17
Table of individual data Physiological saline
Experiment IV

Study Code:	21/071-038CS															Strain:	ROSS 308									
Date of Exposure:	08 June 2021															Negative Control:	Physiological saline (NaCl 0.9% w/v)									
Chamber number ↓	Corneal thickness (instrument units)															Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
10	62	62	0.0%	62	*0.0%*	62	*0.0%*	*0.0%*	63	*1.6%*	63	*1.6%*	63	*1.6%*	*1.6%*	0	0	0	0	0	0	*0.00*	0	0	*0.00*

Note: No morphological effect was observed.

APPENDIX 3

TABLES OF ICE CLASSIFICATION

Table 2.1: ICE classification criteria for corneal thickness:

Mean Corneal Swelling (%)	ICE Class
0 to 5	I
>5 to 12	II
>12 to 18 (>75 min after treatment)	II
>12 to 18 (≤75 min after treatment)	III
>18 to 26	III
>26 to 32 (>75 min after treatment)	III
>26 to 32 (≤75 min after treatment)	IV
>32	IV

Table 2.2: ICE classification criteria for corneal opacity:

Mean Maximum Opacity Score	ICE Class
0.0 – 0.5	I
0.6 – 1.5	II
1.6 – 2.5	III
2.6 – 4.0	IV

Table 2.3: ICE classification criteria for fluorescein retention:

Mean Fluorescein Retention Score at 30 minutes post - treatment	ICE Class
0.0 – 0.5	I
0.6 – 1.5	II
1.6 – 2.5	III
2.6 – 3.0	IV

APPENDIX 4

CLASSIFICATION

Table 3.1: Assessment of the general *IN VITRO* eye irritancy and regulatory UN GHS classification (2019):

The following table is used to identify the probably eye irritancy potential of test items. In the case where the result indicates Non-irritant or Corrosive/Severely Irritating, then the test item can be classified. In all other cases the probable level of irritancy can be reported, but a regulatory *in vivo* rabbit eye irritation test is required for regulatory classification and labelling purposes.

UN GHS Classification	Combinations of the three ICE Classes
No Category	**3×I** **2×I, 1×II** **1×I, 2×II**
No prediction can be made	**Other combinations**
Category 1	**3×IV** **2×IV, 1×III** **2×IV, 1×II*** **2×IV, 1×I*** **Corneal opacity = 3 at 30 min (in at least 2 eyes)** **Corneal opacity = 4 at any time point (in at least 2 eyes)** **Severe loosening of epithelium (in at least 1 eye)**

Remark*: combinations of categories less likely to occur

SUMMARY TABLE FOR UN GHS CLASSIFICATION

Criteria for "No category" (all true)	
3 endpoints classed as I or 2 endpoints classed as I and 1 endpoint classed as II or 2 endpoints classed as II and 1 endpoint classed as I:	True/False
No severe corneal morphological changes:	True/False
Test item was not stuck to the cornea at 240 minutes after the post-treatment rinse:	True/False

Criteria for "Category 1" (one or more true)	
2 or more endpoints classed as IV:	True/False
Corneal opacity = 3 at 30 min (in at least 2 eyes):	True/False
Corneal opacity = 4 at any time point (in at least 2 eyes):	True/False
Severe loosening of epithelium (in at least 1 eye):	True/False

Criteria for "No prediction can be made" (one or two true)	
Based on the endpoints not classifiable for No Category, or for Category 1:	True/False
Particles of test item were stuck to the cornea and could not be washed off during the study:	True/False

APPENDIX 5

HISTORICAL CONTROL FOR ICET STUDIES

(updated: 31 May 2021)

	Maximum corneal swelling at up to 75 min				Maximum corneal swelling at up to 240 min				Maximum corneal opacity change		Fluoresccein retention change		Number of eyes
	Min. Value	Max. Value	Mean	SD	Min. Value	Max. Value	Mean	SD	Min. Value	Max. Value	Min. Value	Max. Value	
Negative control/ Physiological Saline													
Year 2014	-3.2%	3.4%	-0.3%	1.1%	-4.8%	3.4%	-0.6%	1.5%	0.0	0.5	0.0	0.5	115
Year 2015	-1.6%	1.7%	0.0%	0.5%	-1.6%	3.2%	0.0%	0.7%	0.0	0.5	0.0	0.0	126
Year 2016	-1.6%	1.6%	0.1%	0.4%	-3.2%	1.7%	0.1%	0.7%	0.0	0.0	0.0	0.0	76
Year 2017	0.0%	0.0%	0.0%	0.0%	-1.6%	0.0%	0.0%	0.2%	0.0	0.0	0.0	0.0	55
Year 2018	0.0%	0.0%	0.0%	0.0%	-1.6%	1.6%	0.0%	0.4%	0.0	0.0	0.0	0.0	63
Year 2019	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	0.0%	0.2%	0.0	0.0	0.0	0.0	62
Year 2020	-1.6%	1.7%	0.0%	0.8%	-3.2%	1.7%	-0.3%	1.2%	0.0	0.0	0.0	0.0	74
Year 2021	0.0%	3.7%	0.4%	0.9%	0.0%	3.7%	1.0%	1.3%	0.0	0.0	0.0	0.0	20
Period 2014-2021	-3.2%	3.7%	0.0%	0.6%	-4.8%	3.7%	-0.1%	1.0%	0.0	0.5	0.0	0.5	591
Positive control/Imidazole													
Year 2014	-6.6%	25.0%	7.1%	6.1%	-15.9%	35.4%	14.6%	8.7%	3.5	4.0	2.0	3.0	160
Year 2015	6.3%	19.7%	11.5%	2.8%	20.0%	36.7%	28.7%	3.5%	3.5	4.0	2.5	3.0	130
Year 2016	4.8%	15.0%	10.3%	1.9%	18.8%	33.3%	26.9%	2.7%	4.0	4.0	3.0	3.0	90
Year 2017	4.8%	16.7%	10.4%	2.2%	20.6%	33.3%	26.1%	2.6%	4.0	4.0	3.0	3.0	87
Year 2018	6.3%	13.3%	10.6%	1.8%	21.9%	31.7%	26.9%	2.5%	4.0	4.0	3.0	3.0	78
Year 2019	6.3%	16.4%	10.7%	2.1%	23.8%	34.4%	28.1%	2.3%	4.0	4.0	2.5	3.0	81
Year 2020	6.6%	25.0%	12.5%	4.6%	17.7%	40.7%	26.0%	6.2%	3.5	4.0	2.5	3.0	63
Year 2021	15.8%	25.5%	19.8%	3.0%	28.6%	45.3%	37.0%	4.0%	4.0	4.0	3.0	3.0	24
Period 2014-2021	-6.6%	25.5%	10.4%	4.5%	-15.9%	45.3%	24.8%	7.7%	3.5	4.0	2.0	3.0	713

APPENDIX 6

COPY OF THE GLP CERTIFICATE

OGYÉI Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet

Hatósági Ellenőrzési Főosztály

1051 Budapest, Zrínyi utca 3.
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E-mail: ogyei@ogyei.gov.hu
Web: www.ogyei.gov.hu

Ref. no: OGYÉI/-29520-2/2021
Admin.: Dr. Szaller Zoltán

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

Charles River Laboratories Hungary Kft.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **07-11 May 2018.**

This certificate is valid up to 11th of May, 2022.

Dr. Lukács Ferenc József
Digitálisan aláírta: Dr. Lukács Ferenc József
Dátum: 2021.05.06 13:04:14 +02'00'

Dr. Ferenc Lukács
Head of Inspectorate

Note: Translation of the text of the certificate in the header: ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); (“Hatósági Ellenőrzési Főosztály”) - (Inspectorate Division) and at the signature: (“Digitálisan aláírta”) - (Digitally signed); (“Dátum”) - (“Date”).

FINAL REPORT

SAMPLE 1 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Study code: 16/085-005N

Study Director: András Mátyás, M.Sc.

08 July 2016

STUDY DIRECTOR STATEMENT

This study has been performed in accordance with the study plan, the OECD Guidelines for Testing of Chemicals No.: 405 (02nd October 2012), Commission Regulation (EC) No 440/2008, B.5 (L 142, 30 May 2008); OPPTS 870.2400 (EPA 712-C-98-195) August 1998 and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: _____ Date: 08 July 2016

András Mátyás, M.Sc.
Study Director

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Aughinish Alumina Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "SAMPLE 1 Farmed RED MUD – Acute Eye Irritation Study in Rabbits" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 08 July 2016

Szabolcs Gáty, M.Sc.
Senior Director of Operations

QUALITY ASSURANCE STATEMENT

Study Code: 16/085-005N

Study Title: SAMPLE 1 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Test Item: SAMPLE 1 Farmed RED MUD

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
16 March 2016	Study Plan	16 March 2016	16 March 2016
23 March 2016	Treatment	23 March 2016	23 March 2016
21 June 2016	Draft Report	21 June 2016	21 June 2016
08 July 2016	Final Report	08 July 2016	08 July 2016

Signature: Balassa Marietta Date: 08 July 2016

Marietta Balassa, B.Sc.
On behalf of QA

GENERAL INFORMATION

STUDY TITLE:	SAMPLE 1 Farmed RED MUD – Acute Eye Irritation Study in Rabbits
TEST ITEM:	SAMPLE 1 Farmed RED MUD
SPONSOR:	Aughinish Alumina Ltd. Address: Aughinish Island, Askeaton, Co Limerick, V94 V8F7 Ireland Phone: +353 (0)61 604000 +353 (0)61 604242
STUDY MONITOR:	Louise Clune Email: louise.clune@augh.com
STUDY PERFORMED BY:	CiToxLAB Hungary Ltd. Address: H-8200 Veszprém, Szabadságpuszta, Hungary Phone: +36 88-545-300 Fax: +36 88-545-301
STUDY DIRECTOR:	András Mátyás, M.Sc. Email: andras.matyas@hu.citoxlab.com
TEST FACILITY MANAGEMENT:	Alyson Leyshon, M.Sc. – Managing Director Szabolcs Gáty M.Sc. – Senior Director of Operations Jan Praslicka, D.V.M., Ph.D. – Director of Scientific Operations David J. Esdaile M.Sc. – Director of Science and Regulatory Affairs
QUALITY ASSURANCE:	Vanda Gyimesi, M.Sc. – Director of QA Marietta Balassa, B.Sc. – QA inspector
RESPONSIBLE PERSONS:	Erika Matting, M.Sc. – Assistant Scientist István Pásztor, DVM– Veterinary Control Edina Röber, DVM – Veterinary Control Tamás Mészáros, DVM – Head of Pharmacy Animal House Staff Pharmacy Staff

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1. SUMMARY

An acute eye irritation study of the test item SAMPLE 1 Farmed RED MUD was performed in New Zealand White rabbits. The irritation effects of the test item were evaluated according to the Draize method (OECD No.: 405, 2012). Rabbits were treated with analgesic and anaesthetic as per the regulatory guideline. Three animals were used to make the classification.

The test item was placed into the conjunctival sac of the left eye of each animal. The untreated right eye served as control. A single amount of 0.1 g test item was administered as a single dose.

The eyes were examined at 1, 24, 48 and 72 hours after application.

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 271) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 3) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 hours after the application, conjunctival redness (score 1) was noted in the rabbit.
At 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 2 (No: 272) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 2) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 1) was noted in the rabbit.
At 48, 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 3 (No: 270) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 2) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 1), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 hours after the application, conjunctival redness (score 1) was noted in the rabbit.
At 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free.

The general state and behaviour of animals were normal throughout the study period. No mortality occurred during the study. The bodyweights of all rabbits were considered to be within the normal range of variability.

The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows:

	Animal 1	Animal 2	Animal 3
Chemosis	0.33	0.00	0.33
Discharge	0.33	0.00	0.33
Redness	1.00	0.33	0.67
Cornea	0.00	0.00	0.00
Iris	0.00	0.00	0.00

The test item SAMPLE 1 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 1 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 1 Farmed RED MUD does not require classification as an eye irritant.

2. INTRODUCTION

The objective of the study was to determine the acute eye irritation effect of the test item SAMPLE 1 Farmed RED MUD in the New Zealand White Rabbit. The test item was applied as a single dose to the left eye of treated animals. The degree of irritation was scored at specified time intervals. Information derived from this test was used to determine the existence of possible hazards likely to arise from exposure of the eyes and adjacent mucous membranes to the test item. The duration of the study was sufficient to evaluate fully the reversibility or irreversibility of the observed effects.

3. MATERIALS AND METHODS

Start of Experiment:	23 March 2016
End of Experiment:	29 March 2016

3.1. TEST ITEM

Name:	SAMPLE 1 Farmed RED MUD
Batch No.:	2015
Appearance:	Red mud
Purity:	mixture, considered as 100 %
Expiry date:	30 November 2016
Storage conditions:	Room temperature (15-25 ºC, below 70 RH %)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety.

In accordance with OECD requirements, the pH was assessed to identify if it was extreme before application to animals. The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAK MT75 method. The pH was found to be 10.43, so the test item is permitted for use in animal studies.

The test item of a suitable chemical purity, all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Pharmacy of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.2. OTHER MATERIALS

For washing:

Name:	Injekt® Disposable Syringe Luer Solo, 20 mL
Lot No.:	1G11048
Expiry Date:	July 2016
Supplier:	B. Braun Melsungen AG, 34209 Melsungen, Germany

Name:	NaCl (0.9%)
Lot No.:	51642Y05-1
Expiry Date:	March 2018
Produced by:	B. Braun Pharmaceuticals SA, 300264 Timisoara, Romania

Systemic opiate analgesic:

Name:	Bupaq 0.3 mg/mL (buprenorphine)
Batch No.:	0115034AD
Expiry Date:	December 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Topical ocular anaesthetic:

Name:	Humacain 4 mg/mL (oxybuprocaine hydrochloride)
Batch No.:	0470515
Expiry Date:	May 2018
Supplier:	Teva Co., 4042 Debrecen, Hungary

Nonsteroidal anti-inflammatory drug:

Name:	Metacam 5 mg/mL (meloxicam)
Batch No.:	G20806D-06
Expiry Date:	June 2017
Produced by:	Boehringer Ingelheim Vetmedica GmbH, Germany

For euthanasia:

Name:	Ketamidor 100 mg/mL(ketamine)
Batch No.:	0914489 AG
Expiry Date:	August 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Name:	Primazin 2% (xylazine)
Batch No.:	1404117-01
Expiry Date:	May 2016
Produced by:	Alfasan International B.V., Kuipersweg 9, 3449 JA Woerden, The Netherlands

Name:	Euthanimal 40% (pentobarbital sodium)
Lot No.:	1409236-06
Expiry Date:	September 2017
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.3. EXPERIMENTAL ANIMALS

Species and strain:	New Zealand White rabbits
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Justification of strain:	The New Zealand White rabbit is one of the standard strains used for acute irritation toxicity studies.
Animal health:	Only animals in acceptable health condition were used for the test. Both eyes of each animal provisionally selected for testing were examined prior to starting the study. Animals showing eye irritation, ocular defects or pre-existing corneal injury were not used.
Number of animals:	3 animals
Age of animals at treatment:	16 weeks old (young adult)
Sex:	Male
Body weight range	
on the day of treatment:	3592 g – 3978 g
before euthanasia:	3604 g – 4100 g
Date of receipt:	11 February 2016
Acclimatization time:	at least 41 days
Animal identification:	The individual identification was by engraved ear tag. The cages were marked with individual identity cards with information about study code, sex, dose, cage number and individual animal number.

3.4. HUSBANDRY

Animal health:	Only healthy animals were used for the test. The veterinarian certified health status.
Number of animal room:	609
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature during the study:	18.9 – 22.8 °C
Relative humidity during the study:	25 – 72 %
Housing/Enrichment:	Rabbits were individually housed in AAALAC approved metal wire rabbit cages. Cages were of an open wire structure and cages were placed together to allow some social interaction with rabbit(s) in adjoining cages.
Ventilation:	15-20 air exchanges/hour

The temperature and relative humidity values were measured continuously. The measured range was checked at least daily during the acclimatisation and experimental phases.

3.5. FOOD AND FEEDING

Animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., H-5300 Karcag, Madarasi út 0399, Hungary, *ad libitum*. Animals were provided with the following batches:

- Batch No.: 0003003494, expiry date: 17 March 2016
- Batch No.: 0003063492, expiry date: 17 April 2016
- Batch No.: 0003103511, expiry date: 03 May 2016

The details of the diet used will be archived with the raw data and are not reported.

3.6. WATER SUPPLY AND QUALITY CONTROL OF WATER

The animals received municipal tap water, as for human consumption, *ad libitum*, from an automatic system. The quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u. 36., Hungary). The quality control results are retained in the archives of CiToxLAB Hungary Ltd.

3.7. TESTING PROCEDURE

3.7.1. Identification of pH

The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAK MT75 method. The pH was found to be 10.43, so the test item is permitted for use in animal studies.

3.7.2. Pre-study examination

Three male animals in acceptable health condition were selected for the test. Care was taken to select only those animals that had a normal eye condition and any with ocular lesions were rejected.

3.7.3. Chronology of animal use

Initially only one rabbit was treated with test item. The local effects showed scores above zero but not severe, therefore a second rabbit was treated 48 hours after the first rabbit. The result in the second rabbit was not severe; thus a third rabbit was treated after the 24-hour observation of the second rabbit.

3.7.4. Analgesic and anaesthetic treatment

Sixty minutes (60 ±10 min) prior to test substance application, a systemic opiate analgesic was administered subcutaneous injection (SC) under direct Veterinary supervision. Repeat injections were given on the first day as appropriate to maintain an adequate level of analgesia.

Five minutes (5 ±1.5 min) prior to test substance application, a topical ocular anaesthetic was applied to each eye (including the control eye to ensure direct comparison of any ocular observations).

Eight hours (8 to 9 hr) after test substance application, a systemic opiate analgesic and a nonsteroidal anti-inflammatory drug (NSAID) were administered by subcutaneous injection under direct Veterinary supervision. The systemic opiate analgesic was again injected ~12 hours after the post-treatment analgesic and then every 12 hours, and NSAID injected every ~24 hours, until eye scores were zero.

Systemic opiate analgesic: Buprenorphine 0.01 mg/kg.
Topical ocular anaesthetic: Oxybuprocaine one-two drops per eye.
Non-steroidal anti-inflammatory drug: Meloxicam 0.5 mg/kg.

3.8. ADMINISTRATION OF THE TEST ITEM

3.8.1. Dosage

0.1 g of powdered test item SAMPLE 1 Farmed RED MUD was administered as supplied to the animal.

3.8.2. Application of the Test Item

The test substance was placed in the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for at least one second in order to prevent loss of the material.

The untreated contralateral eye served as the control.

3.8.3. Duration of Exposure

As the irritation scores were more than one and test item remained in the eye sac in all animals at the one hour observation time point, the treated eye of test animals was rinsed with physiological saline solution.

3.9. OBSERVATIONS AND SCORING

3.9.1. Clinical Observations and Evaluation of Ocular Irritation

The eyes were examined at 1, 24, 48, 72 hours after treatment. The duration of the observation period was sufficient to identify reversibility or irreversibility of changes. Any clinical signs of toxicity or signs of ill-health during the study were recorded. At the end of the observation period, the animal was sacrificed by intramuscular injections of ketamin 10% (Ketamidor) and xylazin 2% (Primazin 2%) followed by i.v. pentobarbital sodium (see details in 3.2.). Death was verified by checking pupil and corneal reflex and the absence of respiration.

All rabbits were examined for distress at least twice daily, with observations at least 6 hours apart. Clinical observations or signs of ill-health were recorded.

3.9.2. Scoring and Assessment of Local Reaction

The eye irritation scores were evaluated according to the scoring system by Draize (1977) and OECD 405 (02 October 2012) shown in Appendix 1.

3.9.3. Classification of the Test Items

Individual reactions of the animals were recorded at each observation time. The nature, severity and duration of all lesions observed were described.

Results were presented and interpreted according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, amending Regulation (EC) No 1907/2006 and UN Globally Harmonised System of Classification and Labelling of Chemicals, as follows:

Irreversible effects on the eye/serious damage to eyes (Category 1)

Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight.

Category for irreversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days;

and/or

— at least in 2 of 3 tested animals, a positive response of:
  - corneal opacity ≥ 3 and/or
  - iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Reversible effects on the eye/irritating to eyes (Category 2A)

Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Category for reversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in 2 of 3 tested animals, a positive response of:
- corneal opacity ≥ 1 and/or
- iritis ≥ 1, and/or
- conjunctival redness ≥ 2 and/or
- conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

According to the UN GHS (Rev. 6) (2015), within this category an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.

3.9.4. Measurement of Body Weight

Individual body weight was recorded on the day of treatment and at the end of observation period of each animal (Table 3).

4. ARCHIVES

The study documents and samples:
- study plan,
- all raw data,
- sample of the test item,
- study report and any amendment(s),
- correspondence

are stored in the archives of CiToxLAB Hungary Ltd., 8200 Veszprém, Szabadságpuszta, Hungary according to the Hungarian GLP and applicable SOPs.

After the retention (15 years) time has elapsed, all the archived materials listed above will be offered to the Sponsor for further storage or disposal.

5. THE PERMISSION OF THE INSTITUTIONAL IACUC

The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the study plan and authorised the conduct of the study.

6. DEVIATION TO THE STUDY PLAN

The relative humidity (min 25 % and max 72 %) were out of the target range (30-70 %) during the study.

The Draft report was issued later than stated in the Study Plan.

These deviations are considered to have no impact on the outcome of the study and interpretation of the results.

7. RESULTS

7.1. MORTALITY

There was no mortality observed during the study.

7.2. BODY WEIGHTS

The body weight of the animals was considered to be within the normal range of variability. (See Table 3)

7.3. CLINICAL OBSERVATION

7.3.1. General daily examination

There were no clinical signs observed that could be related to treatment.

7.3.2. Examination of eye-irritancy

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 271) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 3) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 hours after the application, conjunctival redness (score 1) was noted in the rabbit.
At 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 2 (No: 272) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 2) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 1) was noted in the rabbit.
At 48, 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 3 (No: 270) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 2) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 1), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 hours after the application, conjunctival redness (score 1) was noted in the rabbit.

At 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free. The general state and behaviour of animals were normal throughout the study period. The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows (See Table 2):

	Animal 1	Animal 2	Animal 3
Chemosis	0.33	0.00	0.33
Discharge	0.33	0.00	0.33
Redness	1.00	0.33	0.67
Cornea	0.00	0.00	0.00
Iris	0.00	0.00	0.00

8. CONCLUSION

The test item SAMPLE 1 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 1 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 1 Farmed RED MUD does not require classification as an eye irritant.

T A B L E S

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION

Study Code: 16/085-005N
Species: NZW Rabbit
Dose: 0.1 g
Sex: Male
Day of Treatment: 23/25/26 March 2016
Test Item: SAMPLE 1 Farmed RED MUD

Abbreviations: R = Redness; CH = Chemosis; D = Discharge; 0 = Normal (in case of control eye and other lesions)
OD = Opacity degree of density; OE = Extent of opaque area; IPR/PR = Initial or any pain reaction

Animal No.: **271**

Time		Score of irritation							IPR/PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	3	0	0	0	0	0	0
	24 h	2	1	1	0	0	0	0	0	0
	48 h	1	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

Animal No.: **272**

Time		Score of irritation							IPR/PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	0	0	0	0	0	0
	24 h	1	0	0	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION (Continued)

Animal No.: **270**

Time		Score of irritation							IPR/ PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	0	0	0	0	0	0
	24 h	1	1	1	0	0	0	0	0	0
	48 h	1	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 2: MEAN VALUES OF EYE IRRITATION
(24, 48, 72 hours reading)

Study Code: 16/085-005N
Species: NZW Rabbit
Dose: 0.1 g
Sex: Male
Day of Treatment: 23/25/26 March 2016
Test Item: SAMPLE 1 Farmed RED MUD

Animal Number	Sex	Cornea Opacity	Iris	Conjunctivae		
				Redness	Chemosis	Discharge
271	male	0.00	0.00	1.00	0.33	0.33
272	male	0.00	0.00	0.33	0.00	0.00
270	male	0.00	0.00	0.67	0.33	0.33

TABLE 3: BODY WEIGHT DATA

Animal Number	Before treatment (g)	Before euthanasia (g)	Body weight gain (g)
271	3592	3604	12
272	3978	4100	122
270	3854	3900	46

APPENDICES

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION

1. Conjunctivae

A. Redness (Palpebral and bulbar)

Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3

B. Chemosis

Normal	0
Some swelling above normal (includes nictating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

C. Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, on considerable area around the eye	3

2. Iris

D. Values

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia: or injection: iris reactive to light (a sluggish reaction is considered to be an effect)	1
Haemorrhage, gross destruction, or no reaction to light.	2

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION (Continued)

3. Cornea

E. Opacity-degree of density (Area most dense taken for reading)

No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre): details of iris clearly visible	1
Easily discernible translucent area: details of iris slightly obscured	2
Nacrous area: no details of iris visible: size of pupil barely discernible	3
Opaque cornea: iris not discernible through the opacity	4

F. Area of cornea involved

One quarter (or less), but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

4. Any other lesions in the eye
(e.g. pannus, staining, anterior chamber changes) text description or 0 if absent

APPENDIX 2:

SCORING OF PAIN REACTION

Class	Reaction by Animal	Descriptive Rating
0	No response	No pain
1	A few blinks only, normal within one or two minutes	Practically no pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate pain
4	Rabbit holds eye shut vigorously, may squeal	Severe pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe pain

NOTE: If an IPR/PR score of 4 or 5 is observed, or if more than transient score 3 is observed, then the rabbit is treated with "rescue analgesia".

APPENDIX 3:

COPY OF THE SPONSOR STATEMENT

Sponsor Statement:
Acute Eye Irritation Study in Rabbits

STUDY CODE: 16/085-005N

TEST ITEM: SAMPLE 1 Farmed RED MUD

	Confirm Each (True or False)
There is no known human or animal data that would prevent this rabbit study being required.	TRUE
There is no SAR data available that would prevent this rabbit study being required (only applies to pure chemicals, not mixtures).	N/A
Chemical reactivity is not expected to cause a severe reaction (i.e. it is not expected to be a strong oxidising agent or reactive amine etc : pH will be measured as part of this study).	TRUE
There is no known evidence that a dose of less than ~20 mg of test item per kg of animal body weight would cause lethal or severe effects.	TRUE
There is no known evidence that the Test Item is corrosive to skin or that it would cause severe eye effects.	TRUE

	Confirm One (Y)
The Sponsor has requested an *in vitro* eye irritation test or will supply the results of such a test to justify that a severe effect is not anticipated.	Y
The Sponsor will supply other information to justify that a severe effect is not anticipated (see below).	
The Sponsor will supply a justification for an alternative Testing Strategy.	

	Confirm (Y or N)
After the first rabbit has been treated and the results are not severe, the second one is treated. The OECD guideline states: "If results from the second animal are sufficient to allow for a hazard classification determination, then no further testing should be conducted". For the specific regulatory purpose of this study, is a 3rd rabbit required unless the result is severe?	N

Herewith, the sponsor declares that the active ingredient as well as the co-formulants contained in the above-mentioned test item do not raise a concern for potential severe eye effects.

ON BEHALF OF SPONSOR : Louise Clune DATE: 9/3/16.

APPENDIX 4:

COPY OF THE CERTIFICATE OF ANALYSIS

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CiToxLAB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

Aughinish Alumina Limited, Aughinish Island, Askeaton, Co Limerick, V94 V8F7 – Ireland
Tel. +353 (0)61 604000 – Fax +353(0)61 604242 – www.rusal.com
DIRECTORS: K Bezzubov, R Bogaudinov, D A Clancy, S Garland, D Goldberg, O Stasev, K Strunnikov, Y Sukhanova
Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

APPENDIX 5:

COPY OF THE GLP CERTIFICATE

OGYÉI
National Institute of Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

FINAL REPORT

SAMPLE 2 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Study code: 16/137-005N

Study Director: András Mátyás, M.Sc.

12 July 2016

STUDY DIRECTOR STATEMENT

This study has been performed in accordance with the study plan, the OECD Guidelines for Testing of Chemicals No.: 405 (02nd October 2012), Commission Regulation (EC) No 440/2008, B.5 (L 142, 30 May 2008); OPPTS 870.2400 (EPA 712-C-98-195) August 1998 and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: _____ Date: 12 July 2016

András Mátyás, M.Sc.
Study Director

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Aughinish Alumina Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "SAMPLE 2 Farmed RED MUD – Acute Eye Irritation Study in Rabbits" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 12 July 2016

Alyson Leyshon, M.Sc.
Managing Director

QUALITY ASSURANCE STATEMENT

Study Code: 16/137-005N

Study Title: SAMPLE 2 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Test Item: SAMPLE 2 Farmed RED MUD

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
25 April 2016	Study Plan	25 April 2016	25 April 2016
26 April 2016	Treatment	26 April 2016	26 April 2016
08 July 2016	Draft Report	08 July 2016	08 July 2016
12 July 2016	Final Report	12 July 2016	12 July 2016

Signature: Merazga Leila Date: 12 July 2016

Leila Merazga, M.Sc.
On behalf of QA

GENERAL INFORMATION

STUDY TITLE:	SAMPLE 2 Farmed RED MUD – Acute Eye Irritation Study in Rabbits
TEST ITEM:	SAMPLE 2 Farmed RED MUD
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STUDY MONITOR:	Louise Clune Email: louise.clune@augh.com
STUDY PERFORMED BY:	CiToxLAB Hungary Ltd. Address: H-8200 Veszprém, Szabadságpuszta, Hungary Phone: +36 88-545-300 Fax: +36 88-545-301
STUDY DIRECTOR:	András Mátyás, M.Sc. Email: andras.matyas@hu.citoxlab.com
TEST FACILITY MANAGEMENT:	Alyson Leyshon, M.Sc. – Managing Director Szabolcs Gáty M.Sc. – Senior Director of Operations Jan Praslicka, D.V.M., Ph.D. – Director of Scientific Operations David J. Esdaile M.Sc. – Director of Science and Regulatory Affairs
QUALITY ASSURANCE:	Vanda Gyimesi, M.Sc. – Director of QA Leila Merazga, M.Sc. – QA inspector
RESPONSIBLE PERSONS:	Máté Weisz, M.Sc. – Assistant Scientist István Pásztor, DVM– Veterinary Control Edina Röber, DVM – Veterinary Control Tamás Mészáros, DVM – Head of Pharmacy Animal House Staff Pharmacy Staff

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1. SUMMARY

An acute eye irritation study of the test item SAMPLE 2 Farmed RED MUD was performed in New Zealand White rabbits. The irritation effects of the test item were evaluated according to the Draize method (OECD No.: 405, 2012). Rabbits were treated with analgesic and anaesthetic as per the regulatory guideline. Three animals were used to make the classification.

The test item was placed into the conjunctival sac of the left eye of each animal. The untreated right eye served as control. A single amount of 0.1 g test item was administered as a single dose.

The eyes were examined at 1, 24, 48 and 72 hours after application.

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 194) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 2 (No: 191) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 3 (No: 390) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free.

The general state and behaviour of animals were normal throughout the study period.
No mortality occurred during the study. The bodyweights of all rabbits were considered to be within the normal range of variability.

The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows:

	Animal 1	Animal 2	Animal 3
Chemosis	0.00	0.00	0.00
Discharge	0.00	0.00	0.00
Redness	0.00	0.00	0.00
Cornea	0.00	0.00	0.00
Iris	0.00	0.00	0.00

The test item SAMPLE 2 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival and corneal effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 2 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 2 Farmed RED MUD does not require classification as an eye irritant.

2. INTRODUCTION

The objective of the study was to determine the acute eye irritation effect of the test item SAMPLE 2 Farmed RED MUD in the New Zealand White Rabbit. The test item was applied as a single dose to the left eye of treated animals. The degree of irritation was scored at specified time intervals. Information derived from this test was used to determine the existence of possible hazards likely to arise from exposure of the eyes and adjacent mucous membranes to the test item. The duration of the study was sufficient to evaluate fully the reversibility or irreversibility of the observed effects.

3. MATERIALS AND METHODS

Start of Experiment:	26 April 2016
End of Experiment:	30 April 2016

3.1. TEST ITEM

Name:	SAMPLE 2 Farmed RED MUD
Batch No.:	2015
Appearance:	Red mud
Purity:	mixture, considered as 100 %
Expiry date:	30 November 2016
Storage conditions:	Room temperature (15-25 ºC, below 70 RH %)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety.

In accordance with OECD requirements, the pH was assessed to identify if it was extreme before application to animals. The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAC MT75 method. The pH was found to be 10.35, so the test item is permitted for use in animal studies.

The test item of a suitable chemical purity, all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Pharmacy of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.2. OTHER MATERIALS

For washing:

Name:	Injekt® Disposable Syringe Luer Solo, 20 mL
Lot No.:	1G11048
Expiry Date:	July 2016
Supplier:	B. Braun Melsungen AG, 34209 Melsungen, Germany

Name:	NaCl (0.9%)
Lot No.:	51642Y05-1
Expiry Date:	March 2018
Produced by:	B. Braun Pharmaceuticals SA, 300264 Timisoara, Romania

Systemic opiate analgesic:

Name:	Bupaq 0.3 mg/mL (buprenorphine)
Batch No.:	0115034AD
Expiry Date:	December 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Topical ocular anaesthetic:

Name:	Humacain 4 mg/mL (oxybuprocaine hydrochloride)
Batch No.:	0470515
Expiry Date:	May 2018
Supplier:	Teva Co., 4042 Debrecen, Hungary

Nonsteroidal anti-inflammatory drug:

Name:	Metacam 5 mg/mL (meloxicam)
Batch No.:	G20806D-06
Expiry Date:	June 2017
Produced by:	Boehringer Ingelheim Vetmedica GmbH, Germany

For euthanasia:

Name:	Ketamidor 100 mg/mL(ketamine)
Batch No.:	0914489 AG
Expiry Date:	August 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Name:	Primazin 2% (xylazine)
Batch No.:	1505130-03
Expiry Date:	May 2017
Produced by:	Alfasan International B.V., Kuipersweg 9, 3449 JA Woerden, The Netherlands

Name:	Euthanimal 40% (pentobarbital sodium)
Lot No.:	1409236-06
Expiry Date:	September 2017
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.3. EXPERIMENTAL ANIMALS

Species and strain:	New Zealand White rabbits
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Justification of strain:	The New Zealand White rabbit is one of the standard strains used for acute irritation toxicity studies.
Animal health:	Only animals in acceptable health condition were used for the test. Both eyes of each animal provisionally selected for testing were examined prior to starting the study. Animals showing eye irritation, ocular defects or pre-existing corneal injury were not used.
Number of animals:	3 animals
Age of animals at treatment:	16 weeks old (young adult)
Sex:	Male
Body weight range	
on the day of treatment:	3709 g – 3885 g
before euthanasia:	3754 g – 3921 g
Date of receipt:	16 March 2016
Acclimatization time:	at least 41 days
Animal identification:	The individual identification was by engraved ear tag. The cages were marked with individual identity cards with information about study code, sex, dose, cage number and individual animal number.

3.4. HUSBANDRY

Animal health:	Only healthy animals were used for the test. The veterinarian certified health status.
Number of animal room:	618
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature during the study:	20.4 – 24.2 °C
Relative humidity during the study:	24 – 70 %
Housing/Enrichment:	Rabbits were individually housed in AAALAC approved metal wire rabbit cages. Cages were of an open wire structure and cages were placed together to allow some social interaction with rabbit(s) in adjoining cages.
Ventilation:	15-20 air exchanges/hour

The temperature and relative humidity values were measured continuously. The measured range was checked at least daily during the acclimatisation and experimental phases.

3.5. FOOD AND FEEDING

Animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., H-5300 Karcag, Madarasi út 0399, Hungary, *ad libitum*. Animals were provided with the following batches:

- Batch No.: 0003063492, expiry date: 17 April 2016
- Batch No.: 0003103511, expiry date: 03 May 2016

The details of the diet used will be archived with the raw data and are not reported.

3.6. WATER SUPPLY AND QUALITY CONTROL OF WATER

The animals received municipal tap water, as for human consumption, *ad libitum*, from an automatic system. The quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u. 36., Hungary). The quality control results are retained in the archives of CiToxLAB Hungary Ltd.

3.7. TESTING PROCEDURE

3.7.1. Identification of pH

The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAC MT75 method. The pH was found to be 10.35, so the test item is permitted for use in animal studies.

3.7.2. Pre-study examination

Three male animals in acceptable health condition were selected for the test. Care was taken to select only those animals that had a normal eye condition and any with ocular lesions were rejected.

3.7.3. Chronology of animal use

Initially only one rabbit was treated with test item. The local effects showed scores zero at 24 hours post-treatment, therefore the second and third rabbits were treated 24 hours after the first rabbit.

3.7.4. Analgesic and anaesthetic treatment

Sixty minutes (60 ±10 min) prior to test substance application, a systemic opiate analgesic was administered by subcutaneous injection (SC) under direct Veterinary supervision. Repeat injections were given on the first day as appropriate to maintain an adequate level of analgesia.

Five minutes (5 ±1.5 min) prior to test substance application, a topical ocular anaesthetic was applied to each eye (including the control eye to ensure direct comparison of any ocular observations).

Eight hours (8 to 9 hr) after test substance application, a systemic opiate analgesic and a nonsteroidal anti-inflammatory drug (NSAID) were administered by subcutaneous injection under direct Veterinary supervision. The systemic opiate analgesic was again injected ~12 hours after the post-treatment analgesic and then every 12 hours, and NSAID injected every ~24 hours, until eye scores were zero.

Systemic opiate analgesic: Buprenorphine 0.01 mg/kg.
Topical ocular anaesthetic: Oxybuprocaine one-two drops per eye.
Non-steroidal anti-inflammatory drug: Meloxicam 0.5 mg/kg.

3.8. ADMINISTRATION OF THE TEST ITEM

3.8.1. Dosage

0.1 g of powdered test item SAMPLE 2 Farmed RED MUD was administered as supplied to the animal.

3.8.2. Application of the Test Item

The test substance was placed in the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for at least one second in order to prevent loss of the material.

The untreated contralateral eye served as the control.

3.8.3. Duration of Exposure

As the irritation scores were more than one and test item remained in the eye sac in all animals at the one hour observation time point, the treated eye of test animals was rinsed with physiological saline solution.

3.9. OBSERVATIONS AND SCORING

3.9.1. Clinical Observations and Evaluation of Ocular Irritation

The eyes were examined at 1, 24, 48, 72 hours after treatment. The duration of the observation period was sufficient to identify reversibility or irreversibility of changes. Any clinical signs of toxicity or signs of ill-health during the study were recorded. At the end of the observation period, the animal was sacrificed by intramuscular injections of ketamin 10% (Ketamidor) and xylazin 2% (Primazin 2%) followed by i.v. pentobarbital sodium (see details in 3.2.). Death was verified by checking pupil and corneal reflex and the absence of respiration.

All rabbits were examined for distress at least twice daily, with observations at least 6 hours apart. Clinical observations or signs of ill-health were recorded.

3.9.2. Scoring and Assessment of Local Reaction

The eye irritation scores were evaluated according to the scoring system by Draize (1977) and OECD 405 (02 October 2012) shown in Appendix 1.

3.9.3. Classification of the Test Item

Individual reactions of the animals were recorded at each observation time. The nature, severity and duration of all lesions observed were described.

Results were presented and interpreted according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, amending Regulation (EC) No 1907/2006 and UN Globally Harmonised System of Classification and Labelling of Chemicals, as follows:

Irreversible effects on the eye/serious damage to eyes (Category 1)

Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight.

Category for irreversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days;

and/or

— at least in 2 of 3 tested animals, a positive response of:
  - corneal opacity ≥ 3 and/or
  - iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Reversible effects on the eye/irritating to eyes (Category 2A)

Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Category for reversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in 2 of 3 tested animals, a positive response of:
- corneal opacity ≥ 1 and/or
- iritis ≥ 1, and/or
- conjunctival redness ≥ 2 and/or
- conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

According to the UN GHS (Rev. 6) (2015), within this category an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.

3.9.4. Measurement of Body Weight

Individual body weight was recorded on the day of treatment and at the end of observation period of each animal (Table 3).

4. ARCHIVES

The study documents and samples:
- study plan,
- all raw data,
- sample of the test item,
- study report and any amendment(s),
- correspondence

are stored in the archives of CiToxLAB Hungary Ltd., 8200 Veszprém, Szabadságpuszta, Hungary according to the Hungarian GLP and applicable SOPs.

After the retention (15 years) time has elapsed, all the archived materials listed above will be offered to the Sponsor for further storage or disposal.

5. THE PERMISSION OF THE INSTITUTIONAL IACUC

The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the study plan and authorised the conduct of the study.

6. DEVIATION TO THE STUDY PLAN

The relative humidity (min 24 %) was out of the target range (30-70 %) during the study.

The temperature (max 24.2 °C) was out of the target range (17-23 °C) during the study.

These deviations are considered to have no impact on the outcome of the study and interpretation of the results.

7. RESULTS

7.1. MORTALITY

There was no mortality observed during the study.

7.2. BODY WEIGHTS

The body weight of the animals was considered to be within the normal range of variability. (See Table 3)

7.3. CLINICAL OBSERVATION

7.3.1. General daily examination

There were no clinical signs observed that could be related to treatment.

7.3.2. Examination of eye-irritancy

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 194) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 2 (No: 191) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 3 (No: 390) clinical observation
At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24, 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free. The general state and behaviour of animals were normal throughout the study period.

The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows (See Table 2):

	Animal 1	Animal 2	Animal 3
Chemosis	0.00	0.00	0.00
Discharge	0.00	0.00	0.00
Redness	0.00	0.00	0.00
Cornea	0.00	0.00	0.00
Iris	0.00	0.00	0.00

8. CONCLUSION

The test item SAMPLE 2 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival and corneal effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 2 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 2 Farmed RED MUD does not require classification as an eye irritant.

T A B L E S

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION

Study Code: 16/137-005N
Species: NZW Rabbit
Dose: 0.1 g
Sex: Male
Day of Treatment: 26/27 April 2016
Test Item: SAMPLE 2 Farmed RED MUD

Abbreviations: R = Redness; CH = Chemosis; D = Discharge; 0 = Normal (in case of control eye and other lesions)
OD = Opacity degree of density; OE = Extent of opaque area; IPR/PR = Initial or any pain reaction

Animal No.: **194**

Time		Score of irritation							IPR/PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	0	0	0	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

Animal No.: **191**

Time		Score of irritation							IPR/PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	0	0	0	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION (Continued)

Animal No.: **390**

Time		Score of irritation							IPR/ PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	0	0	0	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 2: MEAN VALUES OF EYE IRRITATION
(24, 48, 72 hours reading)

Study Code: 16/137-005N
Dose: 0.1 g
Day of Treatment: 26/27 April 2016
Species: NZW Rabbit
Sex: Male
Test Item: SAMPLE 2 Farmed RED MUD

Animal Number	Sex	Cornea Opacity	Iris	Conjunctivae		
				Redness	Chemosis	Discharge
194	male	0.00	0.00	0.00	0.00	0.00
191	male	0.00	0.00	0.00	0.00	0.00
390	male	0.00	0.00	0.00	0.00	0.00

TABLE 3: BODY WEIGHT DATA

Animal Number	Before treatment (g)	Before euthanasia (g)	Body weight gain (g)
194	3885	3917	32
191	3853	3921	68
390	3709	3754	45

APPENDICES

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION

1. Conjunctivae

A. Redness (Palpebral and bulbar)

Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3

B. Chemosis

Normal	0
Some swelling above normal (includes nictating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

C. Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, on considerable area around the eye	3

2. Iris

D. Values

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia: or injection: iris reactive to light (a sluggish reaction is considered to be an effect)	1
Haemorrhage, gross destruction, or no reaction to light.	2

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION (Continued)

3. Cornea

E. Opacity-degree of density (Area most dense taken for reading)

No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre): details of iris clearly visible	1
Easily discernible translucent area: details of iris slightly obscured	2
Nacrous area: no details of iris visible: size of pupil barely discernible	3
Opaque cornea: iris not discernible through the opacity	4

F. Area of cornea involved

One quarter (or less), but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

4. Any other lesions in the eye
(e.g. pannus, staining, anterior chamber changes) text description or 0 if absent

APPENDIX 2:

SCORING OF PAIN REACTION

Class	Reaction by Animal	Descriptive Rating
0	No response	No pain
1	A few blinks only, normal within one or two minutes	Practically no pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate pain
4	Rabbit holds eye shut vigorously, may squeal	Severe pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe pain

NOTE: If an IPR/PR score of 4 or 5 is observed, or if more than transient score 3 is observed, then the rabbit is treated with "rescue analgesia".

APPENDIX 3:

COPY OF THE SPONSOR STATEMENT

Sponsor Statement:
Acute Eye Irritation Study in Rabbits

STUDY CODE: 16/137-005N

TEST ITEM: SAMPLE 2 Farmed RED MUD

	Confirm Each (True or False)
There is no known human or animal data that would prevent this rabbit study being required.	TRUE
There is no SAR data available that would prevent this rabbit study being required (only applies to pure chemicals, not mixtures).	N/A
Chemical reactivity is not expected to cause a severe reaction (i.e. it is not expected to be a strong oxidising agent or reactive amine etc : pH will be measured as part of this study).	TRUE
There is no known evidence that a dose of less than ~20 mg of test item per kg of animal body weight would cause lethal or severe effects.	TRUE
There is no known evidence that the Test Item is corrosive to skin or that it would cause severe eye effects.	TRUE

	Confirm One (Y)
The Sponsor has requested an *in vitro* eye irritation test or will supply the results of such a test to justify that a severe effect is not anticipated.	Y
The Sponsor will supply other information to justify that a severe effect is not anticipated (see below).	
The Sponsor will supply a justification for an alternative Testing Strategy.	

	Confirm (Y or N)
After the first rabbit has been treated and the results are not severe, the second one is treated. The OECD guideline states: "If results from the second animal are sufficient to allow for a hazard classification determination, then no further testing should be conducted". For the specific regulatory purpose of this study, is a 3rd rabbit required unless the result is severe?	N

Herewith, the sponsor declares that the active ingredient as well as the co-formulants contained in the above-mentioned test item do not raise a concern for potential severe eye effects.

ON BEHALF OF SPONSOR : [signature] DATE: 21/4/16

APPENDIX 4:

COPY OF THE CERTIFICATE OF ANALYSIS

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CiToxLAB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

Aughinish Alumina Limited, Aughinish Island, Askeaton, Co Limerick, V94 V8F7 – Ireland
Tel. +353 (0)61 604000 – Fax +353(0)61 604242 – www.rusal.com
DIRECTORS: K Bezzubov, R Bogaudinov, D A Clancy, S Garland, D Goldberg, O Stasev, K Strunnikov, Y Sukhanova
Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

APPENDIX 5:

COPY OF THE GLP CERTIFICATE

OGYÉI
National Institute of Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

FINAL REPORT

SAMPLE 3 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Study code: 16/138-005N

Study Director: András Mátyás, M.Sc.

12 July 2016

STUDY DIRECTOR STATEMENT

This study has been performed in accordance with the study plan, the OECD Guidelines for Testing of Chemicals No.: 405 (02nd October 2012), Commission Regulation (EC) No 440/2008, B.5 (L 142, 30 May 2008); OPPTS 870.2400 (EPA 712-C-98-195) August 1998 and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: _____ Date: 12 July 2016

András Mátyás, M.Sc.
Study Director

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Aughinish Alumina Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "SAMPLE 3 Farmed RED MUD – Acute Eye Irritation Study in Rabbits" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 12 July 2016

Alyson Leyshon, M.Sc.
Managing Director

QUALITY ASSURANCE STATEMENT

Study Code: 16/138-005N

Study Title: SAMPLE 3 Farmed RED MUD – Acute Eye Irritation Study in Rabbits

Test Item: SAMPLE 3 Farmed RED MUD

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
25 April 2016	Study Plan	25 April 2016	25 April 2016
26 April 2016	Treatment	26 April 2016	26 April 2016
08 July 2016	Draft Report	08 July 2016	08 July 2016
12 July 2016	Final Report	12 July 2016	12 July 2016

Signature: Merazga Leila Date: 12 July 2016

Leila Merazga, M.Sc.
On behalf of QA

GENERAL INFORMATION

STUDY TITLE:	SAMPLE 3 Farmed RED MUD – Acute Eye Irritation Study in Rabbits
TEST ITEM:	SAMPLE 3 Farmed RED MUD
SPONSOR:	Aughinish Alumina Ltd. Address: Aughinish Island, Askeaton, Co. Limerick, V94 V8F7 Ireland Phone: +353 (0)61 604000 +353 (0)61 604242
STUDY MONITOR:	Louise Clune Email: louise.clune@augh.com
STUDY PERFORMED BY:	CiToxLAB Hungary Ltd. Address: H-8200 Veszprém, Szabadságpuszta, Hungary Phone: +36 88-545-300 Fax: +36 88-545-301
STUDY DIRECTOR:	András Mátyás, M.Sc. Email: andras.matyas@hu.citoxlab.com
TEST FACILITY MANAGEMENT:	Alyson Leyshon, M.Sc. – Managing Director Szabolcs Gáty M.Sc. – Senior Director of Operations Jan Praslicka, D.V.M., Ph.D. – Director of Scientific Operations David J. Esdaile M.Sc. – Director of Science and Regulatory Affairs
QUALITY ASSURANCE:	Vanda Gyimesi, M.Sc. – Director of QA Leila Merazga, M.Sc. – QA inspector
RESPONSIBLE PERSONS:	Máté Weisz, M.Sc. – Assistant Scientist István Pásztor, DVM– Veterinary Control Edina Röber, DVM – Veterinary Control Gábor Boros, DVM – Veterinary Control Tamás Mészáros, DVM – Head of Pharmacy Animal House Staff Pharmacy Staff

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1. SUMMARY

An acute eye irritation study of the test item SAMPLE 3 Farmed RED MUD was performed in New Zealand White rabbits. The irritation effects of the test item were evaluated according to the Draize method (OECD No.: 405, 2012). Rabbits were treated with analgesic and anaesthetic as per the regulatory guideline. Three animals were used to make the classification.

The test item was placed into the conjunctival sac of the left eye of each animal. The untreated right eye served as control. A single amount of 0.1 g test item was administered as a single dose.

The eyes were examined at 1, 24, 48 and 72 hours after application.

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 198) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1), discharge (score 1) and corneal opacity (score 1, area 2) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 2 (No: 386) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2) and chemosis (score 1) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

Animal 3 (No: 387) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed.

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free.

The general state and behaviour of animals were normal throughout the study period.

No mortality occurred during the study. The bodyweights of all rabbits were considered to be within the normal range of variability.

The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows:

	Animal 1	Animal 2	Animal 3
Chemosis	0.33	0.33	0.33
Discharge	0.33	0.00	0.33
Redness	0.67	0.67	0.67
Cornea	0.33	0.00	0.00
Iris	0.00	0.00	0.00

The test item SAMPLE 3 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival and corneal effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 3 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 3 Farmed RED MUD does not require classification as an eye irritant.

2. INTRODUCTION

The objective of the study was to determine the acute eye irritation effect of the test item SAMPLE 3 Farmed RED MUD in the New Zealand White Rabbit. The test item was applied as a single dose to the left eye of treated animals. The degree of irritation was scored at specified time intervals. Information derived from this test was used to determine the existence of possible hazards likely to arise from exposure of the eyes and adjacent mucous membranes to the test item. The duration of the study was sufficient to evaluate fully the reversibility or irreversibility of the observed effects.

3. MATERIALS AND METHODS

Start of Experiment:	26 April 2016
End of Experiment:	02 May 2016

3.1. TEST ITEM

Name:	SAMPLE 3 Farmed RED MUD
Batch No.:	2015
Appearance:	Red mud
Purity:	mixture, considered as 100 %
Expiry date:	30 November 2016
Storage conditions:	Room temperature (15-25 ºC, below 70 RH %)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety.

In accordance with OECD requirements, the pH was assessed to identify if it was extreme before application to animals. The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAC MT75 method. The pH was found to be 10.54, so the test item is permitted for use in animal studies.

The test item of a suitable chemical purity, all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Pharmacy of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.2. OTHER MATERIALS

For washing:

Name:	Injekt® Disposable Syringe Luer Solo, 20 mL
Lot No.:	1G11048
Expiry Date:	July 2016
Supplier:	B. Braun Melsungen AG, 34209 Melsungen, Germany

Name:	NaCl (0.9%)
Lot No.:	51642Y05-1
Expiry Date:	March 2018
Produced by:	B. Braun Pharmaceuticals SA, 300264 Timisoara, Romania

Systemic opiate analgesic:

Name:	Bupaq 0.3 mg/mL (buprenorphine)
Batch No.:	0115034AD
Expiry Date:	December 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Topical ocular anaesthetic:

Name:	Humacain 4 mg/mL (oxybuprocaine hydrochloride)
Batch No.:	0470515
Expiry Date:	May 2018
Supplier:	Teva Co., 4042 Debrecen, Hungary

Nonsteroidal anti-inflammatory drug:

Name:	Metacam 5 mg/mL (meloxicam)
Batch No.:	G20806D-06
Expiry Date:	June 2017
Produced by:	Boehringer Ingelheim Vetmedica GmbH, Germany

For euthanasia:

Name:	Ketamidor 100 mg/mL(ketamine)
Batch No.:	0914489 AG
Expiry Date:	August 2017
Produced by:	Richterpharma AG, 4600 Wels, Austria

Name:	Primazin 2% (xylazine)
Batch No.:	1505130-03
Expiry Date:	May 2017
Produced by:	Alfasan International B.V., Kuipersweg 9, 3449 JA Woerden, The Netherlands

Name:	Euthanimal 40% (pentobarbital sodium)
Lot No.:	1409236-06
Expiry Date:	September 2017
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.3. EXPERIMENTAL ANIMALS

Species and strain:	New Zealand White rabbits
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Justification of strain:	The New Zealand White rabbit is one of the standard strains used for acute irritation toxicity studies.
Animal health:	Only animals in acceptable health condition were used for the test. Both eyes of each animal provisionally selected for testing were examined prior to starting the study. Animals showing eye irritation, ocular defects or pre-existing corneal injury were not used.
Number of animals:	3 animals
Age of animals at treatment:	16 weeks old (young adult)
Sex:	Male
Body weight range	
on the day of treatment:	3832 g – 3951 g
before euthanasia:	3891 g – 3997 g
Date of receipt:	16 March 2016
Acclimatization time:	at least 41 days
Animal identification:	The individual identification was by engraved ear tag. The cages were marked with individual identity cards with information about study code, sex, dose, cage number and individual animal number.

3.4. HUSBANDRY

Animal health:	Only healthy animals were used for the test. The veterinarian certified health status.
Number of animal room:	618
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature during the study:	19.6 – 24.2 °C
Relative humidity during the study:	22 – 70 %
Housing/Enrichment:	Rabbits were individually housed in AAALAC approved metal wire rabbit cages. Cages were of an open wire structure and cages were placed together to allow some social interaction with rabbit(s) in adjoining cages.
Ventilation:	15-20 air exchanges/hour

The temperature and relative humidity values were measured continuously. The measured range was checked at least daily during the acclimatisation and experimental phases.

3.5. FOOD AND FEEDING

Animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., H-5300 Karcag, Madarasi út 0399, Hungary, *ad libitum*. Animals were provided with the following batches:

- Batch No.: 0003063492, expiry date: 17 April 2016
- Batch No.: 0003103511, expiry date: 03 May 2016
- Batch No.: 0003236234, expiry date: 04 July 2016

The details of the diet used will be archived with the raw data and are not reported.

3.6. WATER SUPPLY AND QUALITY CONTROL OF WATER

The animals received municipal tap water, as for human consumption, *ad libitum*, from an automatic system. The quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u. 36., Hungary). The quality control results are retained in the archives of CiToxLAB Hungary Ltd.

3.7. TESTING PROCEDURE

3.7.1. Identification of pH

The pH of the test item was measured from the supernatant of the 1% w/v aqueous test item formulation by Mettler Toledo Seven Easy™ laboratory pH-meter according to CIPAC MT75 method. The pH was found to be 10.54, so the test item is permitted for use in animal studies.

3.7.2. Pre-study examination

Three male animals in acceptable health condition were selected for the test. Care was taken to select only those animals that had a normal eye condition and any with ocular lesions were rejected.

3.7.3. Chronology of animal use

Initially only one rabbit was treated with test item. The local effects showed scores above zero but not severe, therefore a second rabbit was treated 48 hours after the first rabbit. The result in the second rabbit was not severe; thus a third rabbit was treated after the 24-hour observation of the second rabbit.

3.7.4. Analgesic and anaesthetic treatment

Sixty minutes (60 ±10 min) prior to test substance application, a systemic opiate analgesic was administered by subcutaneous injection (SC) under direct Veterinary supervision. Repeat injections were given on the first day as appropriate to maintain an adequate level of analgesia.

Five minutes (5 ±1.5 min) prior to test substance application, a topical ocular anaesthetic was applied to each eye (including the control eye to ensure direct comparison of any ocular observations).

Eight hours (8 to 9 hr) after test substance application, a systemic opiate analgesic and a nonsteroidal anti-inflammatory drug (NSAID) were administered by subcutaneous injection under direct Veterinary supervision. The systemic opiate analgesic was again injected ~12 hours after the post-treatment analgesic and then every 12 hours, and NSAID injected every ~24 hours, until eye scores were zero.

Systemic opiate analgesic: Buprenorphine 0.01 mg/kg.
Topical ocular anaesthetic: Oxybuprocaine one-two drops per eye.
Non-steroidal anti-inflammatory drug: Meloxicam 0.5 mg/kg.

3.8. ADMINISTRATION OF THE TEST ITEM

3.8.1. Dosage

0.1 g of powdered test item SAMPLE 3 Farmed RED MUD was administered as supplied to the animal.

3.8.2. Application of the Test Item

The test substance was placed in the conjunctival sac of the left eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for at least one second in order to prevent loss of the material.

The untreated contralateral eye served as the control.

3.8.3. Duration of Exposure

As the irritation scores were more than one and test item remained in the eye sac in all animals at the one hour observation time point, the treated eye of test animals was rinsed with physiological saline solution.

3.9. OBSERVATIONS AND SCORING

3.9.1. Clinical Observations and Evaluation of Ocular Irritation

The eyes were examined at 1, 24, 48, 72 hours after treatment. The duration of the observation period was sufficient to identify reversibility or irreversibility of changes. Any clinical signs of toxicity or signs of ill-health during the study were recorded. At the end of the observation period, the animal was sacrificed by intramuscular injections of ketamin 10% (Ketamidor) and xylazin 2% (Primazin 2%) followed by i.v. pentobarbital sodium (see details in 3.2.). Death was verified by checking pupil and corneal reflex and the absence of respiration.

All rabbits were examined for distress at least twice daily, with observations at least 6 hours apart. Clinical observations or signs of ill-health were recorded.

3.9.2. Scoring and Assessment of Local Reaction

The eye irritation scores were evaluated according to the scoring system by Draize (1977) and OECD 405 (02 October 2012) shown in Appendix 1.

3.9.3. Classification of the Test Item

Individual reactions of the animals were recorded at each observation time. The nature, severity and duration of all lesions observed were described.

Results were presented and interpreted according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, amending Regulation (EC) No 1907/2006 and UN Globally Harmonised System of Classification and Labelling of Chemicals, as follows:

Irreversible effects on the eye/serious damage to eyes (Category 1)

Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight.

Category for irreversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days;

and/or

— at least in 2 of 3 tested animals, a positive response of:
  - corneal opacity ≥ 3 and/or
  - iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Reversible effects on the eye/irritating to eyes (Category 2A)

Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Category for reversible eye effects
If, when applied to the eye of an animal, a substance produces:
— at least in 2 of 3 tested animals, a positive response of:
- corneal opacity ≥ 1 and/or
- iritis ≥ 1, and/or
- conjunctival redness ≥ 2 and/or
- conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

According to the UN GHS (Rev. 6) (2015), within this category an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects listed above are fully reversible within 7 days of observation.

3.9.4. Measurement of Body Weight

Individual body weight was recorded on the day of treatment and at the end of observation period of each animal (Table 3).

4. ARCHIVES

The study documents and samples:
- study plan,
- all raw data,
- sample of the test item,
- study report and any amendment(s),
- correspondence

are stored in the archives of CiToxLAB Hungary Ltd., 8200 Veszprém, Szabadságpuszta, Hungary according to the Hungarian GLP and applicable SOPs.

After the retention (15 years) time has elapsed, all the archived materials listed above will be offered to the Sponsor for further storage or disposal.

5. THE PERMISSION OF THE INSTITUTIONAL IACUC

The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the study plan and authorised the conduct of the study.

6. DEVIATION TO THE STUDY PLAN

The relative humidity (min 22 %) was out of the target range (30-70 %) during the study or acclimation period.

The temperature (max 24.2 °C) was out of the target range (17-23 °C) during the study or acclimation period.

These deviations are considered to have no impact on the outcome of the study and interpretation of the results.

7. RESULTS

7.1. MORTALITY

There was no mortality observed during the study.

7.2. BODY WEIGHTS

The body weight of the animals was considered to be within the normal range of variability. (See Table 3)

7.3. CLINICAL OBSERVATION

7.3.1. General daily examination

There were no clinical signs observed that could be related to treatment.

7.3.2. Examination of eye-irritancy

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

Animal 1 (No: 198) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1), discharge (score 1) and corneal opacity (score 1, area 2) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 2 (No: 386) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2) and chemosis (score 1) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

Animal 3 (No: 387) clinical observation

At one hour after the application, conjunctival redness (score 2), chemosis (score 2), discharge (score 2) and corneal opacity (score 1, area 4) were noted in the rabbit. Test item remained in the eye sac at 1 hour observation time point.
At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1) were noted in the rabbit.
At 48 and 72 hours after the application, no clinical signs, and no conjunctival or corneal effects were observed. (See Table 1)

As no clinical signs were observed, the experiment was terminated after 72 hours observation. During the experiment, the control eye of each animal was symptom-free. The general state and behaviour of animals were normal throughout the study period. The animals' individual mean scores (considering readings at 24, 48 and 72 hours after the treatment) were as follows (See Table 2):

	Animal 1	Animal 2	Animal 3
Chemosis	0.33	0.33	0.33
Discharge	0.33	0.00	0.33
Redness	0.67	0.67	0.67
Cornea	0.33	0.00	0.00
Iris	0.00	0.00	0.00

8. CONCLUSION

The test item SAMPLE 3 Farmed RED MUD, applied to rabbit eye mucosa, caused conjunctival and corneal effects at one hour after application which were fully reversible within 72 hours.

According to Regulation (EC) No 1272/2008, SAMPLE 3 Farmed RED MUD does not require classification as an eye irritant.

According to the UN Globally Harmonised System of Classification and Labelling of Chemicals, SAMPLE 3 Farmed RED MUD does not require classification as an eye irritant.

T A B L E S

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION

Study Code: 16/138-005N
Species: NZW Rabbit
Dose: 0.1 g
Sex: Male
Day of Treatment: 26/28/29 April 2016
Test Item: SAMPLE 3 Farmed RED MUD

Abbreviations: R = Redness; OD = Opacity degree of density; CH = Chemosis; OE = Extent of opaque area; D = Discharge; IPR/PR = Initial or any pain reaction; 0 = Normal (in case of control eye and other lesions)

Animal No.: **198**

Time		Score of irritation							IPR/ PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	2	1	1	1	2	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

Animal No.: **386**

Time		Score of irritation							IPR/ PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	2	1	0	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 1: INDIVIDUAL SCORES FOR OCULAR IRRITATION (Continued)

Animal No.: **387**

Time		Score of irritation							IPR/ PR	Other sign
		Conjunctivae			Cornea		Iris	Control eye		
		R	CH	D	OD	OE	R			
Pre-treatment		0	0	0	0	0	0	0	0	0
Post-treatment (h = hour)	1 h	2	2	2	1	4	0	0	0	Test item remained in the eye
	24 h	2	1	1	0	0	0	0	0	0
	48 h	0	0	0	0	0	0	0	0	0
	72 h	0	0	0	0	0	0	0	0	0

TABLE 2: MEAN VALUES OF EYE IRRITATION
(24, 48, 72 hours reading)

Study Code: 16/138-005N
Species: NZW Rabbit
Dose: 0.1 g
Sex: Male
Day of Treatment: 26/28/29 April 2016
Test Item: SAMPLE 3 Farmed RED MUD

Animal Number	Sex	Cornea Opacity	Iris	Conjunctivae		
				Redness	Chemosis	Discharge
198	male	0.33	0.00	0.67	0.33	0.33
386	male	0.00	0.00	0.67	0.33	0.00
387	male	0.00	0.00	0.67	0.33	0.33

TABLE 3: BODY WEIGHT DATA

Animal Number	Before treatment (g)	Before euthanasia (g)	Body weight gain (g)
198	3951	3960	9
386	3929	3997	68
387	3832	3891	59

A P P E N D I C E S

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION

1. Conjunctivae

A. Redness (Palpebral and bulbar)

Normal	0
Some blood vessels hyperaemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse beefy red	3

B. Chemosis

Normal	0
Some swelling above normal (includes nictating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

C. Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, on considerable area around the eye	3

2. Iris

D. Values

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia: or injection: iris reactive to light (a sluggish reaction is considered to be an effect)	1
Haemorrhage, gross destruction, or no reaction to light.	2

APPENDIX 1:

SCORING AND ASSESSMENT OF LOCAL REACTION (Continued)

3. Cornea

E. Opacity-degree of density (Area most dense taken for reading)

No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal lustre): details of iris clearly visible	1
Easily discernible translucent area: details of iris slightly obscured	2
Nacrous area: no details of iris visible: size of pupil barely discernible	3
Opaque cornea: iris not discernible through the opacity	4

F. Area of cornea involved

One quarter (or less), but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

4. Any other lesions in the eye
(e.g. pannus, staining, anterior chamber changes) text description or 0 if absent

APPENDIX 2:

SCORING OF PAIN REACTION

Class	Reaction by Animal	Descriptive Rating
0	No response	No pain
1	A few blinks only, normal within one or two minutes	Practically no pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate pain
4	Rabbit holds eye shut vigorously, may squeal	Severe pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe pain

NOTE: If an IPR/PR score of 4 or 5 is observed, or if more than transient score 3 is observed, then the rabbit is treated with "rescue analgesia".

APPENDIX 3:

COPY OF THE SPONSOR STATEMENT

Sponsor Statement:
Acute Eye Irritation Study in Rabbits

STUDY CODE: 16/138-005N

TEST ITEM: SAMPLE 3 Farmed RED MUD

	Confirm Each (True or False)
There is no known human or animal data that would prevent this rabbit study being required.	TRUE
There is no SAR data available that would prevent this rabbit study being required (only applies to pure chemicals, not mixtures).	N/A
Chemical reactivity is not expected to cause a severe reaction (i.e. it is not expected to be a strong oxidising agent or reactive amine etc : pH will be measured as part of this study).	TRUE
There is no known evidence that a dose of less than ~20 mg of test item per kg of animal body weight would cause lethal or severe effects.	TRUE
There is no known evidence that the Test Item is corrosive to skin or that it would cause severe eye effects.	TRUE

	Confirm One (Y)
The Sponsor has requested an *in vitro* eye irritation test or will supply the results of such a test to justify that a severe effect is not anticipated.	Y
The Sponsor will supply other information to justify that a severe effect is not anticipated (see below).	
The Sponsor will supply a justification for an alternative Testing Strategy.	

	Confirm (Y or N)
After the first rabbit has been treated and the results are not severe, the second one is treated. The OECD guideline states: "If results from the second animal are sufficient to allow for a hazard classification determination, then no further testing should be conducted". For the specific regulatory purpose of this study, is a 3rd rabbit required unless the result is severe?	N

Herewith, the sponsor declares that the active ingredient as well as the co-formulants contained in the above-mentioned test item do not raise a concern for potential severe eye effects.

ON BEHALF OF SPONSOR : Rosanne Chan DATE: 21/9/16

APPENDIX 4:

COPY OF THE CERTIFICATE OF ANALYSIS

RUSAL
AUGHINISH

Below are the Aughinish Alumina analyses of the 3 process samples dispatched to CiToxLAB

	SAMPLE 1 Farmed RED MUD, batch No. 2015	SAMPLE 2 Farmed RED MUD, batch No. 2015	SAMPLE 3 Farmed RED MUD, batch No. 2015
Date	Q1 2015	Q2 2015	Q3 2015
Compound		Wet Basis w/w%	
Moisture	21.9	23.3	23.3
Hematite	17.3	17.0	15.6
Aluminium Goethite	23.0	22.5	23.1
Calcium Cancrinite	12.2	12.0	9.9
Gibbsite	4.2	4.1	3.3
Bayer Sodalite	5.7	5.6	7.4
Perovskite	4.1	4.0	4.6
Anatase and Rutile	4.1	4.1	4.0
Hydrogarnet	3.0	3.0	4.6
Boehmite	2.5	2.5	2.8
Quartz	0.6	0.6	0.5
Sodium Carbonate	0.28	0.34	0.68
Zircon	0.30	0.29	0.30
Gypsum	0.10	0.10	0.20
Carbonate Apatite	0.20	0.25	0.40
Sodium Sulphate	0.05	0.05	0.09
Sodium BiCarbonate	0.01	0.34	0.04
Sodium Fluoride	0.01	0.01	0.01
Sodium Aluminate	0.01	0.07	0.07
Sodium Hydroxide	0	0	0
pH	10.8	11.2	11.4

Product Stability and Expiry Date:

- The products above are red mud by product from the Bayer process for the extraction of alumina from bauxite. The liquid phase consists of dilute sodium aluminate
- The sample are stable at room temperature when stored in sealed containers
- For good measure the proposed sample expiry date is November 2016

Analysis completed by: Bernard Loughlin (Laboratory Manager)

Date: 30/10/15

Aughinish Alumina Limited, Aughinish Island, Askeaton, Co Limerick, V94 V8F7 – Ireland
Tel. +353 (0)61 604000 – Fax +353(0)61 604242 – www.rusal.com
DIRECTORS: K Bezzubov, R Bogaudinov, D A Clancy, S Garland, D Goldberg, O Stasev, K Strunnikov, Y Sukhanova
Reg. in Ireland No.59982. Reg. Office: Aughinish Island, Askeaton, Co Limerick, Ireland

APPENDIX 5:

COPY OF THE GLP CERTIFICATE

OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

APPENDIX

D NATURALLY OCCURING RADIOACTIVE MATERIAL – LABORATORY TEST RESULTS



Radiological Protection Institute of Ireland

An Institiúid Éireannach um Chosaint Raideolaíoch

Radiological assessment of NORM Industries in Ireland – Radiation doses to workers and members of the public

RADIATION UNITS

Radioactivity is measured in units called becquerels (Bq). One becquerel corresponds to one radioactive disintegration per second.

When measuring radioactive discharges to the environment or referring to the content of radioactive sources used in medicine, industry and education, it is more usual to talk in terms of kilobecquerels (kBq), megabecquerels (MBq), gigabecquerels (GBq) or terabecquerels (TBq)

1 kBq = 1000 Bq
1 MBq = 1,000,000 Bq
1 GBq = 1,000,000,000 Bq
1 TBq = 1,000,000,000,000 Bq

Much lower concentrations of radioactivity are normally found in the environment and so the measurement is often reported in units of millibecquerels (mBq). There are one thousand millibecquerels in a becquerel.

1 Bq = 1000 mBq

Radiation Dose When radiation interacts with body tissues and organs, the radiation dose received is a function of factors such as the type of radiation, the part of the body affected, the exposure pathway, etc. This means that one becquerel of radioactivity will not always deliver the same radiation dose. A unit called 'effective dose' has been developed to take account of the differences between different types of radiation so that their biological impact can be compared directly. Effective dose is measured in units called sieverts (Sv).

The sievert is a large unit, and in practice it is more usual to measure radiation doses received by individuals in terms of fractions of a sievert.

1 sievert = 1000 millisievert (mSv)
= 1,000,000 microsievert (μSv)
= 1,000,000,000 nanosievert (nSv)

In RPII reports the term 'effective dose' is often referred to as 'radiation dose' or simply 'dose'.

Collective dose is the sum of the radiation doses received by each individual in the population. This allows comparison of the total radiation dose received from different sources. Collective dose is reported in units of man sieverts (man Sv) or man millisieverts (man mSv).
Per caput dose is the collective dose divided by the total population. Per caput dose is reported in units of sieverts, or fractions of a sievert.

Radiological assessment of NORM Industries in Ireland – Radiation doses to workers and members of the public

Catherine Organo and David Fenton

December 2008

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1 Executive Summary

Natural resources that are extracted from the ground such as coal, oil, natural gas and other mineral ores contain various amounts of natural radioactivity. When these resources are extracted and processed, their natural state can be modified which may result in the enhancement of the natural radioactivity content originally present. Such enhancements may be observed in the residues or the waste created and/or in the products or by-products and are sometimes high enough to pose a risk to both humans and the environment if they are not controlled properly. Materials of this kind are commonly referred to as Naturally Occurring Radioactive Materials or NORM.

Up to 1996, international regulatory attention dealing with exposure to natural sources of radiation focused mostly on exposures arising from the mining and processing of uranium ores because such activities need to be controlled as part of the nuclear fuel cycle. More recently, the attention of the international radiation protection community has been broadened to include industries dealing with NORM. The most recent revision of the European Basic Safety Standards (BSS) Directive took place in 1996 and includes special provisions concerning exposure to natural sources of ionising radiation.

The implementation of the 1996 European Directive resulted in significant legal changes in Ireland. Previously the national radiation protection regulations did not cover work activities involving exposure to natural sources. This changed on 13th May 2000 and according to current Irish regulations, work activities involving exposure to natural sources of radiation such as NORM are amenable to control if they are liable to give rise to an effective dose to workers or members of the public in excess of 1 mSv above background in any 12-month period.

To assist Member States in the implementation of the 1996 European Directive with regards to the provisions dealing with natural sources of radiation, recommendations on how to target only those industries with potential NORM issues were first published by the European Commission in 1997 and were followed by more specific guidance documents covering particular aspects to NORM: building materials, remediation of contaminated sites, NORM effluents and discharges, waste types produced by industries dealing with special metal and ceramics and NORM waste management and treatment options. Countries located outside Europe may follow and/or implement the International Atomic Energy Agency (IAEA) Safety Standards requirements. As far as the identification of work activities involving NORM is concerned, the IAEA has equally produced a number of important and very helpful documents in the recent years, complementary to those published by the EC which capture the essential aspects of the approach advocated by the IAEA to identify NORM industries.

Four large industries operating in Ireland and dealing with NORM were prioritised and investigated to determine the level of radiation to which workers and members of the public were exposed as a result of their work practices: the peat-fired power production, the coal-fired power production, the extraction of natural gas and the bauxite refining for the production of alumina.

In each case, a thorough examination of the industrial process has been carried out to identify the potential radiation exposure situations arising from the occurrence of NORM

at different stages of the respective process. At the core of our assessment methodology, the following aspects were targeted:

- the potential for enhancement of radionuclide concentrations above their natural levels in products, by-products, residues and waste;
- their availability to be released into the biosphere, due to physicochemical changes during processing or due to the method used to manage the residues and the waste produced.

Occupational radiation doses were estimated based on field measurements and analysis of samples collected onsite. For particular scenarios, exposure of members of the public were also considered: exposure to building materials containing peat and coal ash used by the construction industry, exposure to effluents discharged in the atmosphere (coal) and in rivers (peat, coal, bauxite) as well as exposure to radon for domestic gas users. Results were compared to national and international radiation protection standards to determine if any of these four industries needed to be controlled from a radiological point of view.

None of the four industries reviewed was found liable to give rise to an effective dose to workers or members of the public in excess of 1 mSv above background in any 12-month period. As such they do not come under the scope of the Irish regulations, as far as ionising radiation is concerned. Compared to the situation in other countries, this is a very positive outcome which will need to be reviewed in the future and particular areas have already been identified for this purpose.

2 Introduction

Radioactivity of natural origin is present everywhere, in the ground we walk on, in the air we breathe and in the water we drink. As a result, exposure to natural sources of radiation is responsible for about 90 per cent of the total radiation dose received by Irish people every year [Colgan *et al.*, 2008]. Although the level of activity varies considerably with the type of environment and the location, exposures to natural sources of radiation are, with the exception of radon, normally not amenable to control.

Natural resources extracted from the ground such as coal, oil, natural gas and other mineral ores also contain various amounts of natural radioactivity. When these resources are extracted and processed, their natural state can be modified which may result in the enhancement of the natural radioactivity content originally present in the material. Such enhancements may be observed in the residues or in the waste created by the process, in the products or in the by-products and can sometimes be high enough to pose a risk to both humans and the environment if they are not controlled properly. Materials of this kind are commonly referred to as Naturally Occurring Radioactive Materials or NORM.

The International Atomic Energy Agency (IAEA) defines NORM as a "radioactive material containing no significant amounts of radionuclides other than naturally occurring radionuclides" and includes "materials in which the activity concentrations of the naturally occurring radionuclides have been changed by a process" [IAEA, 2007]. Additionally, a NORM residue is defined as a "material that remains from a process and comprises or is contaminated by NORM". A NORM residue may or may not be considered as a waste depending if it is reused and/or recycled.

Investigations of four large industries operating in Ireland have been carried out to assess the extent of exposures of workers directly involved in dealing with NORM as well as members of the public. In each case, the objective was to determine if any of these work activities needed to be regulated as specified in Irish law [Ireland, 2000] as explained in the third chapter of this report. The identification process of those NORM industries where radiological issues might be present is dealt with in chapters four and five and chapter six contains industry-specific assessments. In each case, a review of the industrial process and potential radiation exposures arising from the occurrence of NORM at different stages of the process is given. Dose calculations were carried out based on field measurements and analysis of samples collected onsite. For particular scenarios, exposures of members of the public were also assessed. The doses received as a result of the work activities carried out by each industry were compared with the national and international standards of radiation protection for workers and members of the public and are summarised in the final chapter.

3 European and Irish Legislative Frameworks

In Europe, radiation protection standards to control exposures to all sources of radiation are revised approximately every ten to fifteen years. Up to 1996, international regulatory attention dealing with exposure to natural sources of radiation has been focused mostly on exposures arising from the mining and processing of uranium ores because such activities need to be controlled as part of the nuclear fuel cycle. More recently, the attention of the international radiation protection community has been broadened to include industries dealing with NORM, in recognition of their potential to also give rise to significant exposures to workers and members of the public, thereby implying that they could also be regarded as amenable to control. Some examples of specific situations requiring such attention might include [IAEA, 2003]:

- Cases where industries are producing such a large amount of waste that it becomes unsustainable over time;
- Cases where hazards from natural radionuclides having a long life are increased by their high radiotoxicity;
- Cases where there is a higher likelihood for members of the public to be exposed to NORM wastes and products.

The most recent revision of the European Basic Safety Standards (BSS) Directive took place in 1996 [European Commission, 1996] and includes special provisions concerning exposure to natural sources of ionising radiation. It sets down a framework for controlling work activities where the presence of natural radiation sources could lead to a significant increase in exposure to workers or members of the public which cannot be disregarded from the radiation protection point of view.

The implementation of the 1996 Council Directive resulted in significant legal changes in Ireland. Previously the national radiation protection regulations did not cover work activities involving exposure to natural sources. This changed on 13th May 2000 with the enactment of S.I. 125 of 2000 [Ireland, 2000] which sets out national radiation protection regulations of both practices and other work activities[1] where the presence of natural radioactivity leads to the risk of a significant increase in exposure to workers or members of the public.

From a practical point of view, Article 32 (1) of S.I. 125 of 2000 provides for the regulation of work activities where the presence of natural sources of radiation is liable to give rise to an effective dose to workers or members of the public in excess of 1 mSv above background in any 12-month period. This dose limit is exclusive of radon gas

[1] A practice is defined as a human activity that can increase the exposure of individuals to radiation from an artificial source or from a natural radiation source where natural radionuclides are processed for their radioactive, fissile or fertile properties, except in the case of an emergency exposure [European Commission, 1996; IAEA, 1996a (para. 2.1); Ireland, 2000]. A corollary of this is that a work activity can be defined as a human activity that can increase the exposure of individuals to radiation from a natural radiation source but where natural radionuclides are not processed for their radioactive, fissile or fertile properties.

which is treated separately and for which S.I. 125 of 2000 sets a national Reference Level of 400 Bq/m^3 in the working environment.

The responsibility for identifying activities and working conditions where it is appropriate to regard doses from natural sources of radiation as amenable to control lies with the regulatory authority responsible for the implementation of the 1996 Council Directive in each Member State. As the national regulatory authority, the Radiological Protection Institute of Ireland (RPII) is the competent authority for S.I. 125 of 2000 and for identifying those work activities which, according to European and international guidance, are liable to result in an increased exposure to natural radiation sources and for investigating the extent of this exposure.

4 European and International Guidance on NORM

4.1 Identifying industries with potential NORM radiological issues

To assist Member States in the implementation of the 1996 Council Directive with regards to the provisions dealing with natural sources of radiation, recommendations on how to target only those industries with potential NORM issues were first published by the European Commission in 1997 [European Commission, 1997]. National inventory of NORM activities through site surveys are advocated to identify the circumstances in which the use and storage of materials, not generally regarded as radioactive, could nevertheless give rise to significant doses depending on the activity concentration of the material involved but also on any chemical or physical processing which may increase the availability of the material.

Other documents have been published by the European Commission (EC) covering some more specific aspects to NORM such as building materials [European Commission, 1999a], remediation of sites contaminated by past or old practices or work activities [European Commission, 1999b and 2001b], NORM effluents and discharges [European Commission, 2003], waste types produced by industries dealing with special metal and ceramics [Harvey *et al.*, 1994] and NORM waste management and treatment options [Scholten, 1996 and Wiegers *et al.*, 2000].

Countries located outside Europe may follow and/or implement the IAEA Safety Standards requirements. As far as the identification of work activities involving NORM is concerned, the IAEA has produced a number of important and helpful documents in the recent years, complementary to those published by the EC. The most recent of these, Safety Reports Series No. 49 [IAEA, 2006] captures the essential aspects of the approach advocated by the IAEA to identify NORM industries.

4.2 Regulating: when and what?

Once the NORM industries to be investigated have been identified, the next step is to determine if there is a need to regulate or not. This requires an investigation to determine if any worker or member of the public is liable to receive an annual effective dose from natural sources of radiation arising from the operation of this industry in excess of the statutory dose limit of 1 mSv [Ireland, 2000].

Undertaking a complete dose assessment which takes into account all the exposure pathways and scenarios requires some form of modelling based on reasonable assumptions. As far as possible these assumptions need to represent the real situation to avoid false estimations of the dose received and more importantly to avoid taking the wrong decision with regards to regulating or not [Wymer, 2007].

To simplify the dose assessment process, the EC has produced a simple set of reference values which can specifically be used to determine the extent of the dose received by workers dealing with NORM [European Commission, 1999c and d]. Based on generic scenarios and very conservative assumptions, these documents offer a simple technique

for screening and categorising the relevant NORM industries by relating radiation dose criteria to measurable reference levels in terms of activity concentrations of the feed material or of enhanced activity concentrations in materials at different stages of the industrial process. Additionally, together with Hofmann *et al.* [2000] and Martin *et al.* [1997] these publications identify relevant pathways, typical exposure situations and include a comprehensive review of NORM industries within the European Union, taking into account their potential radiological hazards, their scale and their economic significance.

Generic exemption levels for practices are included in Schedule 5 of S.I. 125 of 2000 and are based on the concept of triviality of risk of exposure, as defined in the Basic Safety Standards of the IAEA [IAEA, 1996a], which is associated with a dose of 10 μSv in a year and a collective dose criterion of approximately 1 manSv/y. While they are applicable for practices dealing with artificial radionuclides or with natural radionuclides when these are processed in view of their radioactive fissile or fertile properties, they are not applicable to work activities dealing with bulk or large quantities of natural radionuclides as it is the case for NORM industries. Indeed, if one excludes radon gas, the range of doses resulting from terrestrial natural radiation lies between a few hundred μSv/y to a few mSv/y. Therefore, applying dose criteria of 10 μSv/y and 1 manSv/y for exposure to natural sources of radiation could bring large areas of the world under regulatory control and it would not be practicable to implement a control scheme for such a small increment to the natural radiation background, which is, in fact, below the natural variability.

An attempt was made by the EC to provide for exemption/clearance levels (Table 1) calculated in terms of activity concentrations specifically applicable to natural sources of radiation [European Commission, 2001a]. Contrary to the exemption levels for practices, scenarios involving large quantities of materials were used and for each scenario one or more pathways were included.

The IAEA advocates applying the same radiation protection standards for artificial and natural radionuclides but with the view that they should relate to the optimisation principle [ICRP, 1991] rather than to the concept of trivial dose used for regulating practices [Wymer, 2007 and IAEA, 1996a, para. 2.8]. As a starting point for exemption, it suggests using the activity concentration specified in the Standards [IAEA, 2004] below which it is usually unnecessary to regulate irrespective of the quantity of material and whether it is in its natural state or has been subject to some form of processing (Table 1). For those industries dealing with materials that are exceeding the suggested exemption values, the same procedure as outlined in Radiation Protection 107 [European Commission, 1999d] is then used by the IAEA [IAEA, 2006] to calculate the doses arising from exposure to various types of material with different activity concentrations (mSv/y per Bq/g). These calculations are based on the same range of exposure situations as Radiation Protection 107 but more realistic assumptions are made. For example, radon exposure is excluded from the dose calculations on the basis that radon concentrations in large scale industries such as NORM industries are usually below the legal action/reference level due to the existence of good ventilation standards [Wymer, 2007].

4.3 Industries with potential NORM issues

Lists of specific industries where NORM may be a problem have been published by the EC and the IAEA. Classified roughly in descending order of priority, the following industrial sectors would require attention [IAEA, 2006]:

- Extraction of rare earth elements
- Production and use of thorium and its compounds
- Production of niobium and ferro-niobium
- Mining of ores other than uranium ore
- Production of oil and gas
- Manufacture of titanium dioxide pigments
- Phosphate industry
- Zircon and zirconia (zirconium oxide) industries
- Production of tin, copper, aluminium, zinc, lead, and iron and steel (smelters)
- Combustion of coal
- Water treatment

In terms of industrial processes, these industries usually fall in one of the following categories [IAEA, 2006]:

- Mining and comminution[2] of ore
- Physical mineral separation processes
- Wet chemical extraction processes
- Thermal processes for extraction, processing and combustion of minerals
- Residue management

Additionally and based on information gathered in the literature, the types of materials handled and/or produced by NORM industries which might have to be considered from a radiological point of view are:

- Feedstocks (raw material)
- Bulk residues
- Slags
- Scales, sludges and sediments
- Precipitator dust
- Intermediate products
- Products

Only some of the above mentioned industries are currently operating in Ireland and taking into account their size as well as their economical significance, it was decided to prioritise our investigations on the following industries:

- Peat-fired power production
- Coal-fired power production
- Natural gas extraction
- Bauxite refining (first step in aluminium production)

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[2] Comminution is the breaking or grinding up of a material to form smaller particles.

5 Radiological Issues in NORM Industries

5.1 Radionuclides of interest

The naturally occurring radioactive elements of interest as far as NORM are concerned belong to the two natural decay series of U-238 and Th-232 (Figure 1 and 2). The third natural decay series led by U-235 is usually not considered in radiological assessments for NORM because it is less abundant than U-238.

When they are left undisturbed for a sufficient amount of time, the daughter radionuclides in each of the chains reach an equilibrium state with the parent such that the activity concentration of each member of the decay series is the same. This state is called secular equilibrium. Disturbances to this equilibrium can arise naturally but also through human activities such as those taking place in NORM industrial processes and they are due to the different physical and chemical properties of the element to which individual decay products are related to. It is these disturbances that are responsible for the radioactivity enhancement or depletion observed in NORM industrial processes. For example, Ra-226 in the U-238 decay series is soluble in water and chemically very different from uranium. By emitting alpha particles, it produces radon (Rn-222), an inert gas that does not react chemically but can escape via gaseous pathways. Lead (Pb) and polonium (Po) which are produced further down the U-238 chain are highly volatile and this is the reason why Pb-210 and Po-210 activity concentrations can be enhanced in compounds which are volatile at high temperatures, making it possible for them to escape by airborne routes. They can also subsequently be adsorbed onto respirable aerosols, thus depositing and contaminating local surfaces as well as lungs.

5.2 Exposure pathways

Individuals are exposed to radiation in different ways and these are commonly referred to as exposure pathways. Relevant exposure pathways to be taken into account in NORM studies are the following:

- External exposure to gamma radiation
- Internal exposure through dust inhalation
- Internal exposure through ingestion
- Skin contamination (from material deposited directly on the skin).

Occupational exposures occur when workers come into close and prolonged contact with NORM materials or inhale dust generated during the process. This can occur when the industrial process itself takes place but also during maintenance operations. Based on studies carried out in a range of industries, the most common routes of exposure from the processes involving naturally occurring radionuclides tend to be external gamma radiation, for example from large quantities or piles of stored material or from residues deposited inside process equipment, and inhalation of dust [IAEA, 2005].

Inhalation of re-suspended radioactivity can occur when someone breathes dust-loaded air with NORM-containing particles that have been re-suspended into the air, for example when the material is transported, broken up or dumped at a landfill. Inhalation doses are estimated on the basis of dust concentrations, breathing rates and radionuclides' concentrations in the fine dust fraction. Dose calculations related to inhalation of furnace fume and precipitator dust usually only take into account Pb-210 and Po-210 because of their volatile properties [Döring *et al.*, 2005, European Commission, 2003].

It is unlikely for NORM residues and waste to be ingested in a direct way, although dust deposited on the skin can always be inadvertently ingested by workers or members of the public. However, general health and safety legislation and good practice requires that when an industrial process has the potential to produce airborne dust, workers are required to wear personal protective equipment (overcoat, gloves and sometimes masks) to prevent or reduce the risk of contamination through this pathway.

Skin contamination is usually not considered to be relevant in dose assessments related to NORM because they are low specific activity materials.

Exposures of the public may arise from the product(s) of a process, from the atmospheric or liquid discharges, from the re-use of by-product material(s) such as fly ash incorporated into cement and concrete, or from the disposal of solid waste(s). The most important routes of radiation exposure of the public are usually external gamma radiation, inhalation and ingestion [European Commission, 2001a].

The regulation of radon gas in the occupational environment is a separate issue to NORM even though it is also a natural source of radiation. Radon is dealt with in S.I. 125 of 2000 [Ireland, 2000] in a specific manner and accordingly is not included in the estimation of the total effective dose to be compared with the legal dose limit of 1 mSv/y. For this reason, doses from exposure to radon in air are not presented in this report.

5.3 Assessment Methodology

The two important aspects of the potential impact of NORM on human health and the environment are:

- The enhancement of the radionuclides' concentrations above their natural levels in the products, by-products or residues produced
- The enhancement of their availability for release into the biosphere through physicochemical changes or due to the method by which the wastes or residues are managed

Generally, radionuclide activity concentrations observed in natural mineral and raw materials are moderately or non-elevated compared to background levels encountered in all types of rocks or soils. Therefore, the need for regulatory attention is likely to arise more from the mobilisation of radionuclides during the extraction or processing of the raw material, especially if concentrations are increased or if exposure pathways to humans are modified [IAEA, 2006]. Industries affected by the presence of NORM differ

considerably with respect to the type of process, the type of material which is processed, the workplace conditions and the radionuclides involved. These aspects need to be taken into account when evaluating the potential degree of exposure as they can all influence the availability of the material.

When carrying out dose assessments, it is necessary to cover all the exposure situations for all those individuals potentially exposed. Exposure scenarios are designed to link the radioactivity contents in various types of materials with the potential dose(s) received. The scenarios should take account of the various receptors (workers and members of the public) and habits, of the characteristics and types of materials, how they are handled, stored and disposed of. All the various pathways through which a dose can be delivered should also be included.

When the objective is to determine the likelihood of the annual effective dose limit of 1 mSv being exceeded, carrying out an in-depth and fully comprehensive dose assessment is neither justified nor necessary. For each NORM investigation the following steps were completed:

- Review of the available literature dealing with the specific industry to get a general overview of the potential issues;
- Contact the operator and organise meeting(s);
- Agree on a methodology describing the objective(s) of the study and how this will be achieved;
- Collect more accurate and technical information on the process, number of workers involved in specific activities, characteristics of these activities (occupancy, duration, use of personal protective equipment PPE etc.);
- Whenever it is possible, organise the collection of representative samples and carry out onsite measurements;
- Analyse the collected samples in the laboratory;
- Carry out the dose calculations and analyse the results *i.e.* compare with the legal requirements (1 mSv/y dose limit and/or international recommended exemption values);
- Conclusions and recommendations.

6 Industry-Specific Radiological Assessments

6.1 Peat-fired electricity production

Since 2000, peat-fired electricity production in Ireland has changed dramatically due to changes in the regulation of Irish electricity production. As a result, all the existing peat-fired power stations (up to 9 plants) built between 1950 and the early 1980s have been decommissioned and replaced with two new plants which have commenced production between the end of 2004 and the beginning of 2005. Between 2001 and 2003, a collaborative study between the RPII and Trinity College Dublin (TCD) was undertaken to investigate NORM issues at a peat-fired power plant which had produced electricity for some forty years, from 1965 until early 2005[3]. The results of this study have been published elsewhere [Organo *et al.*, 2005] and while they describe a process that has since ceased[4], they are still relevant from a radiological point of view.

6.1.1 The industrial process

With a capacity of 125 MW the studied plant was, at the time the investigation started, the largest peat-fired power station in operation in Ireland, consuming approximately 1.1 to 1.2×10^6 tonnes of raw peat and producing on average 20 to 25×10^3 tonnes of ash every year (i.e. 1/3 of the total amount of ash produced by all the combined peat-fired plants). Over the years, the raw peat had been supplied to the plant from a local bog where it was mechanically harvested, coarsely milled and solar dried. From there it was transported to the plant in light rail convoys made of 15 wagons carrying a total of 75 tonnes of peat. On arrival at the plant two tipplers unloaded each wagon sequentially into a hopper and the peat was transferred by conveyor belts to the three 'bunkers' situated inside the plant. The bunkers acted as an intermediate storage area for the peat before it was sent to the mills. They were each capable of holding a 4-hour supply of peat at any one time and were, without a doubt, the dustiest places in the plant. From the bunkers the peat was transferred to the mills where it was pulverised into a fine dust, blown into the boilers (or furnaces) and burnt in suspension at about 1,000-1,100°C.

Two main types of ash are produced in the process: 5 to 10% of the total ash falls below the furnace to form the 'bottom ash' while the remaining 90 to 95% passes into the flue gas stream as 'fly ash'. This gaseous-particulate mixture is drawn through a series of grit arrestors designed to remove the majority of the fly ash (in the case of the studied power

[3] This plant was decommissioned and replaced by a more efficient 150 MW plant which currently produces approximately 3.5% of the total Irish demand for electricity.

[4] The two new peat-fired power plants use the latest efficient and environmentally friendly technologies and both comply with the recent EC Large Combustion Plant Directive [European Commission, 2001c]. As a way of comparison, the studied power plant consisted of three boiler/turbine units as opposed to one in each of the new plants. Current emissions can therefore be expected to be much smaller and occupational health and safety control measures are also likely to be more efficient as they would have been planned at the design stage.

plant, 90%) as well as any unburned carbon. Only a small fraction of the flue gases which passes through the grit arrestors will contain radionuclides in gaseous form and this is discharged through the stack into the atmosphere.

At the studied power plant, 2/3 of the produced bottom ash was transported in a trailer to a 'dry ash' pile situated a short distance away from the plant. The remaining 1/3 and the totality of the fly ash trapped in the grit arrestors were hydraulically piped out by flexible tubing to two nearby 'wet ash' ponds where the ash was kept in a 50% minimum aqueous environment to minimize the production of airborne particles. A total of approximately five million tonnes of ash have been landfilled on site over the years.

6.1.2 Scenarios and pathways

The primary objective of this investigation was to estimate the total annual effective dose received by workers involved in peat processing and peat ash management activities. Public exposure to radionuclides emitted with the gaseous emissions from the stack was not included in the overall assessment. After an exhaustive review of the industrial process followed by site visits, the number of exposure pathways of relevance from the point of view of an occupational dose assessment were narrowed down to the following two:

- inhalation of peat dust in the bunker area assuming no respiratory protection;
- external gamma radiation at different locations in and around the plant.

Following the first site visit, it was decided not to include the inhalation of peat ash dust on landfill sites arising from the generation of windborne ash because the vast majority of the total ash produced is transferred into a pond which makes it very unlikely to be wind blown. Maintenance duties such as cleaning of the hoppers and freeing blockages in the grit arrestors were also deliberately omitted despite the fact that during these activities workers are in close contact with the fly ash. This was decided on the basis that these activities do not occur very frequently (3 times per year), they are usually completed within a few hours/days to avoid long outage and, more importantly, they are undertaken in wet conditions with extensive personal protective equipment (total overall and full respiratory protection).

To cover all the possible exposure situations, it was assumed that in the future peat fly ash could be recycled and used as an additive in the manufacture of construction materials as is already the case for the coal fly ash [Lyons, 2001]. If the natural radioactivity content of the ash was found to be significant, there could be a potential for an increased radiation exposure to persons occupying buildings constructed with such materials and to workers handling and working with the ash.

6.1.3 Materials and methods

Samples of milled peat, fly ash, bottom ash and liquid effluents from the ash ponds were collected and analysed for their radioactive content and onsite measurements of ambient gamma dose rates at various locations in and around the plant were carried out (Figure 3). Details of the analytical techniques and field equipments used in this

investigation can be found in Organo *et al.* [2005]. To assess the radiological health significance of the potential use of peat ash in building materials, the methodology recommended in Radiation Protection 112 [European Commission, 1999a] was followed, as explained in Organo *et al.* [2005].

6.1.4 Results

The activity concentrations measured in the different samples collected at the studied peat-fired power station were found to be moderately variable in the raw peat but extremely variable in both the fly ash and bottom ash samples (Table 2). Peat is an organic deposit and this is reflected in the low activity concentrations in Th-232 and K-40, two radionuclides characteristic of a detritic influence[5]. The clear disequilibrium observed in the peat samples between U-238 and Ra-226 on the one hand and Pb-210 on the other hand is not surprising as re-distribution of soluble and redox-sensitive elements like radium and uranium are a likely occurrence in soil profiles or deposits undergoing intense weathering such as peat. Atmospheric fallout of Pb-210 could also be a contributor to the observed excess Pb-210.

The elevated Pb-210 activity concentrations measured in the ash samples (Table 2) compared with other radionuclides are linked to the volatile properties of Pb at furnace temperatures. Between the furnace and the grit arrestors the mixture of gas and fly ash passes over banks of tubes containing water or air to give a more efficient removal of the heat prior to discharge into the atmosphere. As the flue gases cool down to about 200 °C, the volatilised elements condense onto fly ash particles resulting in the observed enrichment. Except for Pb-210 in the peat fly ash, the analysed peat and peat ash samples contain lower levels of naturally occurring radionuclides than other NORM materials or even Irish soils (Table 3).

The activity concentrations measured in the effluents were found to be extremely low. Under Irish regulations, there are no specific exemption levels applicable to liquid discharges from NORM industries as is the case for most of the European countries [European Commission, 2003]. However, if the peat-fired power generation was considered to be a practice, the analysed effluents would be exempted under Schedule 5 of S.I. 125 of 2000 [Ireland, 2000].

A single air sampling experiment over an entire working shift was carried out in one of the three bunkers to assess the annual effective dose arising from the inhalation of peat dust which may be received by an employee carrying out dry sweeping duties of spilled peat dust. Bunkers are temporary storage areas which are located indoor and constantly filled with a 4-h supply of milled peat. The airborne dust concentration (total fraction) measured during our experiment at this location was found to be as high as 25.6 mg/m^3 which is significant in terms of occupational dust exposure as the Irish occupational exposure limit (OEL) for nuisance dust is set at 10 mg/m^3 [HSA, 2007].

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[5] A sediment (or deposit) has a detritic origin if at least 50% of its constituents derive from the erosion of previously deposited rocks. Examples of detritic sediments or rocks are sandstone, mudstone, sand and loess.

Based on the activity concentrations measured in the peat dust sampled in the bunker (Table 2) and on the airborne dust concentration, the maximum annual effective dose arising from inhalation received by an employee working in the bunker for 100 hours per year, assuming this employee is not wearing any respiratory protection, is about 0.5 μSv/y (Table 4). These conditions are representative of a worse-case scenario as work in the bunkers is only carried out for short periods of time and personal protective equipment (PPE) including protective clothing and face dust mask (EN 149 PP3) is mandatory.

Ambient gamma dose rate measurements were carried out at various locations around the plant, including disposal areas (Figure 3). The measured values, uncorrected for ambient background ranged from 60 to 70 nGy/h (control measurement outside the perimeter of the plant 70 nGy/h). By subtracting a cosmic contribution of 33 nGy/h [Colgan, 1980 and McAulay and Colgan, 1980], a terrestrial background in the local area of 8 nGy/h [Marsh, 1991] and using a conversion factor of 1 Sv/Gy [UNSCEAR, 2000] estimated annual effective doses from exposure to external gamma radiation were all found to be below 20 μSv/y. While no measurement of external gamma dose rate of terrestrial origin was carried out at locations where peat is harvested, dose rates were calculated on the basis of activity concentrations measured in the raw peat (Table 2) and were found to be lower than the natural ambient background [Organo *et al.*, 2005]. Peat harvesting occurs outdoor in the open air by machinery (shielding effect) and both facial mask and protective clothing are mandatory to protect employees from the windborne peat dust thereby minimising the inhalation pathway.

To assess the radiological health significance of the potential use of peat ash in building materials, an Activity Concentration Index (I) was calculated to convert the specific activity of a building material (Bq/kg) into a measure of radiation dose (mSv) that may be received by an individual occupying a 'model room' constructed from a building material with a specific radioactivity, based on its activity concentrations in Ra-226, Th-232 and K-40 [European Commission, 1999a]. The index I was calculated for all the peat ash samples and a maximum value of 0.15 was found in two cases, one fly ash sample and one bottom ash sample. According to the EC [1999a] an index of 0.5 or less ensures a dose of less than 0.3 mSv per annum and materials falling into this category can be used in bulk in building works without restrictions.

6.1.5 Conclusions

Table 5 summarises all the doses calculated in the course of this study. The total effective dose received by a worker carrying out a combination of work duties involving peat processing and peat ash management is approximately 50 μSv per annum, *i.e.* twenty times less than the maximum allowable radiation dose from practices for members of the public. Therefore this NORM industry does not come under the scope of the Irish regulations. The activity concentrations measured in the peat ash indicate that this material could be recycled as an additive in the manufacture of building materials such as cement and/or concrete without concern for workers involved in the manufacture process itself or for members of the public living in buildings constructed with it.

6.2 Coal-fired electricity production

Coal combustion appears in various lists of NORM industries involving minerals and raw materials that may lead to a significant increase in exposure to natural sources which cannot be disregarded from the radiation protection point of view. With this regard, the lack of a comprehensive review of the coal-fired power generating industry in the Republic of Ireland prompted the setting up of a collaborative study between TCD, the RPII and the Electricity Supply Board (ESB) which started in 2002.

6.2.1 The industrial process

Ireland has only one coal-fired power plant but with a 915 MW total capacity (three units of 305 MW[6]), it is the second largest power plant in the country. It was commissioned in 1979 and it currently supplies approximately 20% of the country's daily electricity requirements. To reach this demand, bituminous coal is imported, mainly from Australia, Indonesia, the USA and Columbia and approximately 2×10^6 tonnes are burnt annually (Photo 1).



Photo 1. Coal yard where the coal is stacked prior to being burnt

The imported coal is first milled and pulverised down to less than 100 μm particle size [Meij, 2003] and is then fed into the furnaces where the combustion temperature is approximately 1,100°C (Figure 4). During combustion most of the mineral matter contained in the coal is fused into a vitrified ash. The lighter particles are commonly referred to as pulverised fly ash (PFA) and represent 85% of the total amount of ash produced. The PFA is carried out of the furnaces by the hot exhaust gases and is

[6] Each of the three 305 MW units consists of one low NO_x boiler (Foster Wheeler Drum type, natural circulation) four coal bunkers (600 tonnes of capacity each), four mills, two electrostatic precipitators (ESPs) and one turbine.

subsequently extracted at 99.5% (in quantity) by electrostatic precipitators (or ESPs). The plant produces 17×10^4 tonnes of PFA each year. Volatilised mineral compounds and the fly ash which are not trapped in the ESPs (0.5%) are released to the atmosphere and constitute what is commonly known as escaping fly ash. The remaining 15% of the total amount of ash produced (heavier particles and unburned organic matter) condense onto the boiler tubes and fall at the bottom of each furnace where it sinters to form the furnace bottom ash. Approximately 3×10^4 tonnes are produced annually.

The PFA collected by the ESPs is pneumatically transferred into silos where it is temporarily stored in dry form. Each year, 1×10^5 tonnes of the produced PFA is sold to a cement company which uses it as a shale substitute in cement products. As a result, almost half of all the Normal Portland cement produced in Ireland contains coal PFA. In the cement mix, the fly ash amounts to approximately 5% in mass while concrete only contains between 0.25 and 1% because cement represents only 5 to 20% of the concrete mix in mass. The fly ash which is sold is transported in sealed tankers. The remaining PFA which is not sold (7×10^4 tonnes each year) as well as the totality of the bottom ash produced are conditioned with water (to reduce the dust emissions) and transported separately in open trucks to a dedicated landfill site situated nearby (Photo 2). The maximum disposal capacity of the coal ash landfill currently in use is 3×10^6 m^3. This represents an accumulation of ash of approximately 10 m high in places.



Photo 2. Coal ash landfill and plant in the background

6.2.2 Radiological issues investigated

In a report published in 2001 [Smith *et al.*, 2001], the then National Radiological Protection Board (NRPB)[7] concluded that the radiological impact of the UK coal-fired electricity generation on the UK population was low and did not warrant the application of radiological controls except in two cases:

- The use of flyash in building materials for which the NRPB calculated an excess dose (i.e. a dose above that received outdoors) arising from the ash component in

[7] The NRPB was merged with the Health Protection Agency (HPA) in April 2005.

building materials containing 30% ash of approximately 600 μSv/y after subtraction of the external background[8]. This dose is within the range of 0.3 to 1 mSv/y within which the EC recommends that controls on the use of such building materials should be considered [European Commission, 1999a].

- The possible occurrence of Pb-210 enriched scales inside boilers (low NO_x type) as reported in Dutch coal-fired power stations [Huijbregts *et al.*, 2000]. In their report, the NRPB conservatively estimated that doses in the region of 100 μSv/y could be received by workers involved in boiler maintenance if a scale with a Pb-210 concentration of 100 Bq/g was present.

The activity concentrations measured in coal and coal ash samples collected at the Irish power plant in 1986, 1988 and 1993 (Table 6) are relatively constant and, most importantly, similar to those published in the UK report (Table 7)[9]. On this basis and assuming similar characteristics between the coal power generation industry in the UK and in Ireland, we have assumed that the NRPB report's conclusions were applicable to the Irish situation and decided to focus our investigation on the use of fly ash in Irish building materials and on the possible occurrence of Pb-210 enriched scales. For completeness, it was also decided to include the unpublished results of a study carried out between 1986 and 1990 by the ESB looking at the offsite radiological impact of the plant's atmospheric emissions.

6.2.3 Materials and methods

Coal and coal ash samples collected at the studied power plant were analysed by gamma spectrometry in TCD. Some of the results from earlier studies (1986, 1988) are included in Table 6 for completeness alongside results of more recent measurements specifically carried out for the purpose of this assessment. Details of the gamma spectrometry analysis technique used by TCD can be found in Organo *et al.* [2005]. The radiological health significance of the inclusion of coal fly ash in Irish building materials was investigated according to the methodology recommended in Radiation Protection 112 [European Commission, 1999a] and is described in more details in Lee *et al.* [2004] and Lee [2006]. Samples of residues collected inside one of the boilers of the studied plant (Photo 3) were analysed by the RPII using a p-type GEM gamma ray detector with a relative efficiency of 38.9% and 1.75 keV resolution at 1.33 MeV and a n-type HPGe GMX gamma detector with a relative efficiency of 40.5% and 1.89 keV resolution at 1.33 MeV. Liquid effluents from the ash landfill site collected at the discharge point (Photo 4) were also analysed using a n-type HPGe GMX gamma ray detector of 29% relative efficiency and 1.88 keV resolution at 1.33 MeV.

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[8] 218 μSv/y due to radon and 382 μSv/y due to external gamma radiation.

[9] Activity concentrations in coal fly ash can vary considerably depending on the origin of the coal. The doses reported here are specific to the coal presently being burnt in Ireland. If in the future coal is sourced from other international markets, then its radioactive content may differ and the estimated doses to workers and the public will need to be revised.



Photo 3. **One of the 16 burners inside one of the furnace where boiler residues** (white patches around the opening) **were collected**



Photo 4. **Discharge point of the effluent**

Between 1986 and 1990, an assessment of the offsite radiological impact of the studied power plant in terms of radionuclides dispersion in the plume released from the stack was carried out by the ESB at the request of the Nuclear Energy Board (NEB), the predecessor of the RPII. The model chosen by the ESB at the time was used to model SO_2 emissions and was validated by An Foras Forbartha (which later became the Environmental Protection Agency or EPA).

6.2.4 Results

The activity concentrations measured in the various types of coal supplied at the power plant under investigation (Table 6) are very similar to those encountered in other countries (Table 7). As far as fly ash is concerned (Table 6), results are significantly higher than indicated in the UK (Table 7), particularly for the U-238 decay series. The reason for this has not been identified but it is clear that even when the origin of coal

supplies remains unchanged throughout the years (as it is the case for this plant), the activity concentrations in the coal itself can vary by an order of magnitude.

Coal fly ash contains increased levels of radioactivity compared with those measured in the original coal, typically by an order of magnitude, because combustion of coal results in a 80-95% mass reduction, thus yielding 5-20%[10] ash which contains most of the original radioactive material but now at an enhanced concentration. Radionuclide concentrations in the fly ash can be "predicted" by dividing those measured in the coal by the ash fraction[11] and then compared with activity concentrations measured in the PFA samples. In our case, there is good agreement between the two.

Volatile elements such as Pb-210 and Po-210 usually display higher and highly variable enrichment factors on the smallest particles of escaping fly ash and/or the fly ash trapped in the ESPs [Coles *et al.*, 1979]. Enrichments are radionuclide-specific and depend also largely upon various factors such as the original radioactivity content of the coal, its chlorine and sulphur content, the characteristics of the pulverised fuel (particle size), the type of furnace and the efficiency of the ESPs. Lead-210 and Po-210 were not measured in the Irish coal but an indication that they are not particularly enhanced in the trapped fly ash lies with the apparent absence of radioactive disequilibrium between Ra-226 and Pb-210 in the analysed fly ash (Table 6). Escaping fly ash was not collected for this study because high radioactivity content was not expected. Hence a temporary outage of the plant was not warranted. The potential enrichment of volatile radionuclides onto emitted particles which would indicate a process of volatilisation and preferential condensation onto particles of smaller size was therefore not verified.

Lead-210 was measured in two samples of boiler residues collected inside one of the boilers (Table 6) and an average concentration of 0.4 Bq/g was found. This is well below the activity concentrations which were measured in Dutch boilers and exceeding 100 Bq/g [Huijbregts et al., 2000] and well below both EU and IAEA recommended exemption/exclusion values for Pb-210 in NORM material (Table 1). It means that the radiation dose received by a worker or a member of the public dealing with this type of material would not exceed 0.3 mSv/y.

There are three reasons to explain why the condensation of Pb-210 does not occur in the studied power plant compared to the situation described in the Netherlands [McCarthy, F., personal communication]:

- The lower chlorine content of the coal burnt in the Irish plant; high chlorine contents favour reducing conditions in the boiler which in turn lower the condensation temperature of the lead;
- The boilers used in the Irish plant belong to the first generation of low NO_x boilers; they operate in "naturally reducing" conditions while the Dutch boilers operate in "forced reducing" conditions. In oxidising conditions (Irish boilers), lead is in

[10] The average ash content of the coal burned in the plant investigated here is 10%.

[11] In our case, it means that the radionuclide activity concentrations in the fly ash compared with those in the raw coal can be expected to be multiplied by a factor of 10.

$PbSO_4$ form which has a high condensation point. In the Dutch boilers, lead is present as PbS or $PbCl_2$, both in gaseous form with low condensation points.

- The Irish boilers are smaller than the Dutch ones; therefore the time allotted to particles to react between each other is smaller and, more importantly, the combustion temperature is higher and exceeds the temperature of condensation of lead (880°C).

New low NOx boilers similar to those used in the Netherlands are due to be installed by 2008 to meet the new environmental requirements set by the EU with the possibility that Pb-210 scales could develop over time. Additionally, improved emission control systems (dry desulphurisation system or FGD) to reduce the SO_2 emissions to the atmosphere will also be installed and are likely to result in the production of up to $12x10^4$ tonnes of $CaSO_3$ per year which will have to be landfilled. It is therefore recommended for the future that the radiological consequences of these new operations be investigated.

Two duplicate samples of the liquid effluent collected at the point of discharge originating from the coal ash disposal area were analysed (Table 6) and apart from K-40 which was measured in negligible concentrations, no other radionuclide could be detected by gamma spectrometry.

Cement and concrete containing some amount of the coal fly ash produced by the studied power plant were analysed by TCD and apart from Pb-210, all the other radionuclides had lower activity concentrations than in the raw fly ash (Table 6). Activity concentrations in cement containing fly ash were found to be higher than in concrete containing fly ash. This was expected as greater quantities of fly ash are incorporated into cement compared to concrete[12].

The radiological health significance of the potential use of coal fly ash in Irish building materials was assessed following the methodology recommended by the EU [European Commission, 1999a]. An Activity Concentration Index (I) was calculated for each of the coal fly ash, cement and concrete sample collected for this study and they were all found to be well below the limits of 6 and 2 for superficial materials, implying doses of less than 0.3 mSv/y. Only three fly ash samples had an index greater than the limits of 1 and 0.5 for building materials used in bulk amounts. Although coal fly ash may have higher radioactivity content than other constituents such as sand or aggregates, it is not a building material in itself and it can be considered a “superficial material”. It only constitutes up to 5% of a cement mix so its radioactivity does not impact significantly on the Activity Concentration Index of the final product. The overall increase in the radioactivity levels of cement and concrete containing fly ash is therefore very limited and for this reason coal fly ash can be considered of no radiological health significance if incorporated into Irish building materials. More details on this issue can be found in Lee et al. [2004] and Lee [2006].

Using a model, the ESB calculated the amount of radioactivity discharged by the stack of the studied power plant (source terms) as 2,920 Bq/kg of ash emitted in total alpha and

[12] Concrete only contains fly ash as a result of the inclusion in the concrete mix of cement made with fly ash.

2,409 Bq/kg of ash emitted in total beta (see Appendix A). The ESPs keep the specific emissions of particulate matter well below 50 µg/m^3 which is equivalent to an emission of 13.66 g/s of ash per 305 MW unit. Therefore the total activity emitted was calculated for each 305 MW unit as 2920 x 13.66 = 40 Bq/s total alpha and 2409 x 13.66 = 33 Bq/s total beta. Radon emissions were also calculated using a normal coal throughput for each 305 MW unit of 29.3 kg/s, an average Ra-226 activity concentration in the coal of 30 Bq/kg (Table 6) and assuming 100% volatilisation (gas). The result was calculated as 30 x 29.3 = 879 Bq/s per 305 MW unit.

Ground level concentrations, effectively air concentration at approximately head height were modelled by the ESB using a matrix spatially distributed in a 31 x 41 km grid around the power station and the maximum annual average concentration were 223 nBq/m^3 for the total alpha activity concentration, 184 nBq/m^3 for the total beta activity concentration and 5 µBq/m^3 for the radon activity concentration. Contour maps showing the spatial distributions (or isopleths) of ground level activities were obtained and indicate three areas of maximum concentrations at ground level directly to the North-East, South-East and South-West at a distance of approximately 8.5 to 9 km from the power station.

The maximum annual average radon concentration at ground level calculated by the ESB model (5 µBq/m^3) corresponds to an annual effective dose of 0.05 nSv/y and 0.04 nSv/y for workers and members of the public, respectively[13]. The total alpha and beta activity concentrations at ground level as calculated by the ESB model cannot be transformed directly into inhalation dose as this would require knowing the individual radionuclide activity concentrations at ground level. To estimate these, we used the methodology described in Smith *et al.* [2001] and the results of the calculations in terms of dose to adult members of the public as shown in Table 8 reach a total of 0.02 µSv/y (or 20 nSv/y). As internal exposure to K-40 is excluded from the international regulations [IAEA, 1996a] it was also ignored in this scenario and we used the activity concentrations of the fly ash as measured for this study (Table 6) as opposed to those used by the ESB in their model (see Appendix A). According to Smith *et al.* [2001], the plume inhalation pathway represents approximately 70% of the total dose received by a typical individual from the stack releases. Based on the above calculated inhalation dose, it can be concluded that the overall radiological impact of atmospheric emissions from the studied power station is negligible.

6.2.5 Conclusions

The results reported and discussed in the previous section indicate that, in the context of the Irish regulations, the work activities carried out at the studied coal-fired power station do not give rise to doses liable to exceed 1 mSv to any individual in any 12-month period. Moreover, the recycling of coal fly ash as an additive used in the manufacture of Irish building materials was found to be of no radiological health significance as were the

[13] Using an F factor of 0.6 for outdoor exposure [UNSCEAR, 2000] and an exposure duration of 2000 h/y for workers and 1800 h/y for members of the public.

atmospheric releases resulting from the coal combustion or the liquid discharges from the ash disposal area.

6.3 Natural gas extraction

The only hydrocarbon resource or fossil fuel which is readily and commercially available in Ireland is natural gas. One reservoir is currently in production, since 1978, and it is located offshore in the South West of the country, approximately 15 km off the coast. It produces a dry gas made at 94% of pure methane (density 0.95 g/m^3) and as such it does not need to be treated or heavily processed apart from dehydration which takes place offshore before the gas is sold for distribution to Irish consumers.

6.3.1 The radiological issues linked to the industrial process

Oil and gas reservoirs are rock formations that contain elements such as calcium, strontium, barium and radium. It is not uncommon for these elements to be preferentially dissolved relative to the uranium and thorium which will tend to stay in the reservoirs. When oil and natural gas are extracted, temperature and pressure variations occur that disrupt the chemical balance in the extracted fluids as they are brought to the surface. This eventually may lead to the deposition of residues such as scale or sludge throughout the production equipment. Some of these may show increased radionuclide concentrations, the most common being radium isotopes from both U-238 and Th-232 decay series and their respective decay-products, mostly Pb-210 and Th-228.

One radionuclide of major importance in the gas extracting industry from a radiological point of view is the radon which is released from the reservoir (by diffusion from radium deposits) and is transported with the natural gas to the gas processing plant. During routine operations, as the gas flows continuously through the system and radon gas decays, its short-lived decay-products (Figure 1) tend to plate out on the surfaces that come into contact with the gas stream to form thin dark grey/black films on the internal side of the production equipment [Bjornstad and Ramsoy, 1999]. As these short-lived daughters decay, they emit penetrative gamma radiation which can result in high occupational external gamma radiation doses when working close to the contaminated equipment.

During shut downs for repair, maintenance or cleaning operations, the gas flow stops. Within several hours after the shut down and without a continuous flow bringing new radon gas into the gas stream, radon gas and its short-lived decay-products have decayed and penetrative gamma radiations are no longer emitted. However, the long-lived decay-products of radon (Figure 1) remain in the thin film-like deposits emitting weak gamma radiation and mainly beta and alpha radiation. The energetic alpha emissions of Po-210 and Pb-210, in particular, represent a potential hazard if they become airborne and are ingested or inhaled.

Residues such as sludge are a common occurrence in gas extracting equipment and they usually accumulate in separator vessels, storage tanks, gas lines and other filter assemblies. They mainly contain radium isotopes as well as Pb-210, Bi-210 and Po-210. Scales on the other hand are a rare occurrence in gas production equipment.

6.3.2 Scenarios and pathways investigated

The main pathways by which workers involved in the extraction of natural gas could be exposed to NORM are the following:

- The external gamma radiation from films/coatings of radon short-lived daughters when the equipment is opened for maintenance and during routine operations
- The inhalation of long-lived airborne radionuclides at vessel entries during maintenance or decontamination operations and while handling NORM contaminated parts of equipment
- The inhalation of radon and radon decay-products at vessel entries

During routine operations, significant radiation exposures are unlikely to occur as NORM are mostly contained within pipes and vessels. It is possible however that gamma radiation emitted from radionuclides deposited on the inside of this equipment could pass through the steel walls leading to a potential dose rate at their surface. Personnel carrying out duties on a regular basis in close proximity to such equipment could be unacceptably exposed. These issues were investigated by carrying out radiation surveys of production equipment offshore and onshore (disused equipment) to check for the presence of above background gamma radiation and Pb-210 plating. Radionuclide analysis of NORM residues sampled offshore during maintenance operation was also completed.

The end users of the natural gas extracted in Ireland are members of the public and it is important to investigate the extent of their exposure to the radon which is contained in the gas commercially distributed in the country. The RPII asked the company responsible for the extraction of the gas to carry out a routine monitoring of the radon concentrations in the gas stream for a period of two years. The Physics Department from University College Dublin (UCD) was contracted to carry out the work and radiation doses were calculated by the RPII according to Dixon [2001].

6.3.3 Materials and methods

UCD monitored the radon gas concentrations in the onshore gas stream for a 2-year period (September 2003 to October 2005) using two different techniques of which both detected and recorded alpha particle emissions from radon and its short-lived decay products (Po-218 and Po-214):

- The grab sampling technique: samples of the gas were taken from a suitable pipeline location into previously evacuated 400 cm^3 Lucas cells (Photo 5). The inside of the cell is coated with an alpha particle scintillator (ZnS (Ag)) and at its bottom there is a transparent window. Once a sample is taken and the cell is closed the radon and its short-lived alpha emitting decay products cause scintillations to occur in the ZnS (Ag) scintillation coating. After a period of about 4 hours, in which a state of approximate radioactive equilibrium is reached, the rate of scintillation within the cell reaches its maximum value. The Lucas cell is then placed on top of the photomultiplier in a scintillation counter and the alpha particle scintillation count rate is recorded. The gas filled Lucas cells were

counted in UCD on the day after taking each gas grab sample and the concentrations corrected for the effect of radioactive decay back to the time of sampling.

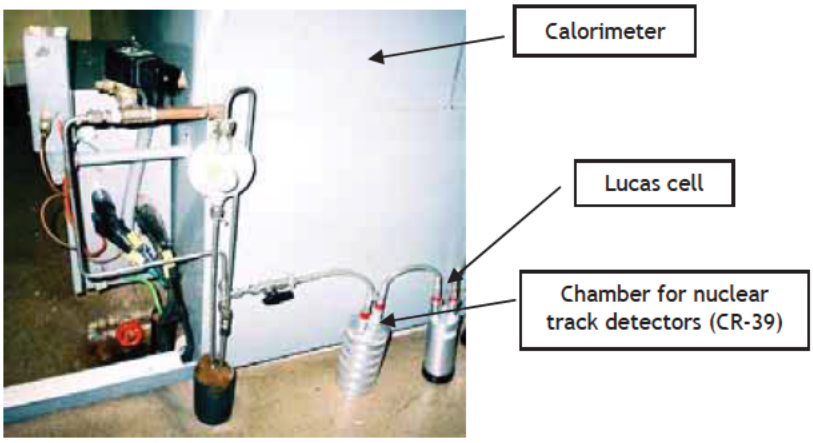


Photo 5. Setup used to monitor the radon concentrations in the gas stream. In this unique experiment, the equipment was setup in the onshore metering station, near the calorimeter. *Photo courtesy of Dr J. McLaughlin (UCD)*

- The continuous monitoring technique: the radon concentrations are integrated over long periods of time (3 and 8 months in our case) using passive SSNTDs (solid state nuclear track detectors), here CR-39. In this experiment, three detectors were placed within a specially fabricated cylindrical aluminium chamber which was attached to the gas line as shown in the photograph above. At the end of the exposure period, the detectors were removed and processed by chemical etching to reveal the alpha tracks caused by radon and its progeny. The tracks were counted by optical microscopy and from the track density data, the mean radon concentration during the exposure period was determined.

Two site visits were conducted, the first one on the offshore platform where the gas is treated directly after extraction and the second one at the warehouse (on the mainland) where the offshore disused equipment is stored. The purpose of these visits was to establish if and where there was a NORM contamination problem at these locations by carrying out ambient gamma dose rates measurements and checking for alpha/beta contamination (Pb-210 plating or invisible scale) inside and outside the equipment to eventually quantify and assess the occupational risk.

Two samples of sludge were collected in two separators on the offshore platform (Photos 6 and 7) and analysed by alpha and gamma spectrometry. This equipment is usually opened, inspected and cleaned once every four years by specialised contractors, using pressurised water jets. From a waste management point of view, the sludge that is left at the bottom of the tanks after cleaning is collected and stored in drums that are sent ashore where the water is drained and the concentrated residue sent to landfill.



Photo 6. One of the 2 separators where the sludge sample was collected



Photo 7. Sludge sample

6.3.4 Results

Table 9 (grab sampling technique), Table 10 (continuous 3-month) and Table 11 (continuous 8-month) as well as Figure 5 summarise the results of the radon gas monitoring as described in the previous section. It is interesting to note that the average radon concentration obtained by the grab sampling technique (638 Bq/m^3) is about 2.5 times greater than the average radon concentration determined by the continuous monitoring method (288 and 265 Bq/m^3 for the 3-month and 8-month measurements, respectively). The reason for this difference is not known but large fluctuations of radon levels over time in natural gas supplies have been recorded for other gas fields [Gesell, 1974].

A study looking at the radon gas concentrations in the commercially distributed gas in the UK showed that for typical rates of gas usage and an average radon concentration of about 200 Bq/m^3, the estimated dose for domestic users of natural gas was only 4 μSv

and for a critical group representing commercial users a few tens of μSv [Dixon, 2001]. Using this relationship, the radiation dose to members of the public in Ireland resulting from exposure at the average radon concentrations measured in the studied natural gas stream (397 Bq/m^3) is about 8 μSv, well below the general 1 mSv/y dose limit for members of the public. To reach this dose limit, a radon concentration of 50,000 Bq/m^3 would be needed. Equally, radon in the gas stream will not be an issue for employees working on the offshore platform or at the onshore terminal because they are never in direct contact with the gas itself as it is always confined and enclosed in production equipment at any point in time.

External gamma radiation fields and contamination signals measured on the offshore platform and at the onshore warehouse were all indistinguishable from the natural background and therefore not considered to be a cause for concern.

The analysis of the two sludge samples (Table 12) show that the activity concentrations are all below the indicative recommended exclusion/exemption values for NORM materials published separately by the EC and the IAEA (Table 1). While these recommendations are not mandatory they both provide guidance for the implementation of the EU and IAEA Basic Safety Standards with regard to natural radiation sources. Estimates were made to assess the annual effective dose received by workers handling the sludge during the cleaning of production equipment. The results of these calculations all indicate that in very conservative conditions (maximum activity concentrations measured, exposure duration of 2000 h/y) the annual effective dose received will be at most around 100 μSv and as such this work activity does not need to be regulated from a radiological point of view.

6.3.5 Conclusions

Radon gas concentrations in the gas stream brought ashore were monitored continuously during a 2-year period. The annual radiation dose to the domestic gas end users resulting from exposure at the measured average radon concentrations was estimated to be about 8 μSv. The radiation dose received by workers involved in the maintenance and cleaning of the offshore equipment was estimated to be at most around 100 μSv per year and the radiation surveys carried out offshore and onshore both indicated that the external gamma radiation fields and contamination signals were indistinguishable from natural background values. From a radiological point of view, it can be concluded that the work activities associated with natural gas extraction in Ireland give rise to doses that are well below the 1 mSv/y statutory limit and as such do not need to be regulated.

6.4 Bauxite refining

Aluminium is the third most abundant element in the Earth's crust but it does not exist in nature in its pure form. Instead, it is chemically bonded with other elements and found in its most concentrated form in bauxite ore, a repository which contains sufficiently high levels of Al_2O_3 and suitably low levels of Fe_2O_3 and silica to be economically exploited. Named after the French district of Les Baux where it was first discovered in 1821,

bauxite is a red deposit produced by tropical or semitropical weathering of alumina-bearing rocks. Bauxite deposits are generally very extensive and found on just about all the continents in the world but the largest known economic resources of bauxite are located in Australia (40%), Guinea, followed by Brazil, Jamaica and India. The US, Japan and Germany are the world's largest consumers of aluminium but they possess little or no bauxite deposits of their own.

The production of aluminium metal takes place in three main stages: the mining of the ore, its refining to recover alumina, and finally the smelting of the alumina (anhydrous aluminium oxide) to produce aluminium. This report deals only with the second stage of this process.

There are approximately thirty bauxite refineries worldwide and six of these are located within the EU. Europe's largest[14] and most recently-built alumina refinery is situated in Ireland. Its construction took place between 1978 and 1983 and was, at the time, the largest construction project in Europe. It was commissioned in 1983 and currently employs approximately 450-500 permanent employees as well as 200 contractors. Ireland does not have a smelting industry and the 1.5×10^6 tonnes of alumina produced each year is shipped to aluminium smelters and other manufacturers mostly in the UK, Scandinavia and elsewhere in Europe.

6.4.1 The industrial process

The site of the Irish bauxite refinery spreads over a total area of 440-hectares of which 150 ha are dedicated to the refining process only. Sixty percent of the 3.5×10^6 tonnes of bauxite ore that are processed annually are imported from Boké in the Republic of Guinea (West Africa) with the remaining 40% being imported from Brazil. The bauxite is shipped in bulk ore carriers, 5×10^3 tonnes at a time, and delivered to the plant's own marine terminal which is located 800 m away from the site. One tanker per week is unloaded on average. From there, the bauxite is transported by conveyor belts and stored in four bulk storage warehouses. The maximum capacity of each warehouse is 15×10^4 tonnes.

In nearly all commercial operations, alumina is produced by the Bayer process[15]. It is a very energy-intensive and large-scale process involving high temperatures and high pressures which consists of four steps:

- Digestion: the finely ground bauxite is digested at a temperature in excess of 250˚C with a hot solution of 4M caustic soda and steam into large pressure vessels or digesters (Photo 8)
- Clarification: the alumina-bearing solution is separated from the insoluble impurities that were part of the original bauxite. These residues are segregated

[14] A refinery in Spain has a similar size to its Irish counterpart. The largest alumina plant in the world is in Queensland (Australia) and is 3 times as big as the Irish refinery.

[15] The Bayer process was discovered by Karl Bayer in 1889 and the first refinery was opened in 1893.

into 10% of sand and 90% of mud, the so-called red mud[16]. The mud is pumped to a purposely built 100-hectare, 20-m high impoundment area also called bauxite residue disposal area (BRDA) where it is stacked up in terraces (Photo 9). The sand is transported by trucks to the BRDA but it is kept separate from the mud

- Precipitation: the alumina is precipitated from the solution as crystals of alumina trihydrate
- Calcination: the alumina trihydrate is washed and heated at over 1,100˚C in special calciners or kilns to obtain the final product, the white sandy alumina



Photo 8. A digester with a skip in front of it containing residues removed after maintenance

[16] Four tonnes of bauxite are required to produce two tonnes of alumina which in turn will produce one tonne of aluminium. In total, every day, approximately $9x10^3$ tonnes of bauxite ore are processed, $4x10^3$ tonnes of alumina generated together with $2x10^3$ tonnes of waste, heat, water effluents and water vapour.



Photo 9. Overview of the bauxite residue disposal area (BRDA) with plant in the background

The refinery currently holds an Integrated Pollution Control Licence (IPCL) issued by the Environmental Protection Agency (EPA). All the environmental aspects of the plant's operation are covered in this IPCL, including emissions to air, water, solid waste, ground water and noise and are closely monitored by the EPA. The IPCL does not cover radiological or radiation protection issues. Any such issue, if raised, would come under the scope of S.I. 125 of 2000 [Ireland, 2000] and would be a matter for the RPII. Therefore the radiological assessment of the Irish bauxite refining industry was carried out to determine if workers or members of the public may receive a dose in excess of 1 mSv in any 12-month period.

6.4.2 Radiological issues investigated

Bauxite ore, the waste products and residues from its refining are not regarded as radioactive materials but if they are not managed properly they could, in theory, have the potential to give rise to a significant increase in radiation exposure of workers and/or members of the public, primarily because of the very large quantities of materials being processed. Maintenance and cleaning of process equipment as well as waste management are, in most cases, the main issues to be investigated as far as NORM are concerned. Experience also shows that when occupational doses from NORM activities are found to be low members of the public are put at no significant risk from these same activities [ICRP, 1997]. Therefore, the following scenarios were investigated:

- Occupational exposure during the maintenance and cleaning of the process equipment where the build-up of residues or scales can take place as a result of the Bayer process. Scales are frequently and routinely removed from the digesters, the flash tanks, the settling tanks (or decanters) and the pipes linking these components. Maintenance work to remove the scales occurs once a year on average at all locations and is specifically carried out by the same contracted workers who are permanently onsite. A range of different techniques are used to remove the scales (pneumatic drills and water pressure jets) which are subsequently gathered in skips and transported by trucks to the BRDA. Removing scales that are encrusted onto steel walls generate large quantities of airborne

dust and particles, and this work usually takes place in confined environment. Therefore, if workers are not sufficiently protected and if the radioactive content of these scales is above an acceptable level, the inhalation of these products could be a significant cause of concern.

- Occupational exposure during waste management activities carried out on the BRDA. If it was left untouched, the accumulated red mud would naturally and slowly dry out. To prevent dusting and avoid the creation of large quantities of airborne red mud particles, the surface of the BRDA is constantly kept slightly damp with a network of sprinklers situated around the site. However, because of the vast quantities of waste that have accumulated since 1983, exposure to non trivial external gamma radiation fields could be a potential hazard for workers and this issue was also investigated.

6.4.3 Materials and methods

Samples of bauxite slurry and scale collected in a digester, a decanter as well as red sand, fresh red mud and runoff water from the BRDA were collected and analysed by high resolution gamma spectrometry by the RPII[17]. The measured activity concentrations were then compared with the IAEA and EU recommended exemption/exclusion values (Table 1). Gamma dose rate measurements were carried out on the BRDA and inside a flash tank during maintenance using a portable Mini-Rad type gamma survey monitor (1000 Series Mini-monitor Type R or 1000R) comprising an energy compensated GM tube with an integration time of 1 to 8 seconds (depending on the dose rate), a measuring range of 0.1 to 1,000 μSv/h and an energy range of 50 keV to 1.25 MeV (±20%).

6.4.4 Results

The results of the gamma spectrometry analysis of the samples collected by the RPII are shown in Table 13. For comparison purposes, published data for similar facilities in other countries are also included. The activity concentrations measured in the red mud are higher than those measured in the original bauxite ore because of the chemical reactions during the refining process which lead to various concentration enhancements, in the Th-232 decay series in particular. Both natural decay series were found to be in radioactive equilibrium in the red mud, while a disequilibrium in the U-238 decay series was found in the bauxite slurry, in the scale collected in the digester and in the red sand. A disequilibrium in the Th-232 decay chain was observed in the scale collected in the digester.

All the measured activity concentrations were found to be below the EC and IAEA indicative recommended exclusion/exemption values for NORM materials (Table 1) which provide some guidance for the implementation of the EU and IAEA Basic Safety

[17] The specifications of the gamma detectors used by the RPII are mentioned in Section 6.2.3 dedicated to the coal-fired electricity production.

Standards with regard to natural radiation sources. Below these concentrations, the radiation dose received by a worker or a member of the public dealing with this type of material is unlikely to exceed 300 μSv/y.

Three different locations were surveyed on the BRDA with regards to the ambient gamma dose rate, two on the red mud and one on the red sand. The average of all the measurements carried out at waist height was 325 nSv/h. A background value of 100 nSv/h was subtracted from this average value[18] to obtain a net average ambient gamma dose rate of 225 nSv/h. As a comparison, external gamma dose rates measured in a red mud pond in Hungary at 1 m above ground ranged from 200 to 400 nSv/h [European Commission, 2007], in total agreement with the values found in the Irish case. Using an average occupancy of 1,800 h/y for employees working on the BRDA [Hartney, 2005], a maximum and very conservative occupational radiation dose from external exposure to gamma radiation of 405 μSv/y was calculated. In comparison, the occupational dose from external gamma radiation received by employees working on a red mud disposal site located in Romania was estimated to be 270 μSv/y [Weiss *et al.*, 2004].

Ambient gamma dose rates were also measured while maintenance work was carried out inside one of the flash tanks. The inside of the tank was scaffolded and two employees, both wearing PPE (overcoat, face mask, hard helmet, gloves, and goggles) were working to remove scales deposited on the inside walls of the tank using pneumatic drills and water-pressure jets. A red-brown scale was found to cover the entire surface of the inside of the tank, between 5 mm and a few cm thick in places and presenting a rather smooth surface. Broken pieces of scale were scattered on the floor. Ambient gamma dose rate measurements were taken at approximately 1 to 2 cm away from the surface of the scale not yet removed as well as inside the inlet and outlet pipes (80 cm in diameter) which would usually be connected to the tank. Scales were found in both pipes, thicker in the outlet pipe. All the readings were found to be between 100 and 200 nSv/h, equivalent to or just marginally above the natural background.

6.4.5 Conclusions

Analysis of red mud samples and direct measurements of external gamma dose rates to which workers are exposed to while carrying out routine and maintenance activities indicate that it is highly unlikely that doses in excess of 1 mSv/y would be received from the work activities carried out and that the bauxite refining industry does not come under the scope of the Irish regulations from a radiological point of view.

[18] Background measurements were carried out outside the perimeter of the refinery and a value ≤ 100 nSv/h was found. The RPII country-wide gamma dose rate monitoring network also recorded an average ambient background gamma dose rate of 85-90 nSv/h during that same period of time.

7 Conclusions

Investigations of four large industries operating in Ireland have been carried out to assess the extent of exposures to natural sources of radiation of the workers involved in these particular industrial processes as well as, in some cases, members of the public, with a view to determine if any of these work activities needed to be regulated as specified by the Irish regulations.

A sector-specific approach to the dose assessments was chosen due to the wide differences in the nature of the industrial processes involved. In each case, a review of the industrial process and potential occupational radiation exposures arising from the occurrence of NORM at different stages of the process has been undertaken. Field measurements and analysis of samples have been used to estimate the radiation doses received by workers directly involved in the handling, processing and storage of NORM.

The results of these investigations are summarised in Table 14 and indicate that none of the work activities reviewed are liable to give rise to an effective dose to workers or members of the public in excess of 1 mSv above background in any 12-month period.

The first decade following the publication of the EU Directive in 1996 to deal with the regulatory aspects of work activities involving NORM and their practical implementation has seen agencies responsible for radiation protection matters in various countries focusing on the identification of those NORM industries which could potentially be of concern. From an early stage, the international community favoured a harmonised approach and many international conferences have been organised to try and fulfil this objective.

Although international consensus around some specific and critical issues is still lacking [Wymer, 2007], this first decade has allowed the international community to better define and identify the areas where real radiological problems might lie. The years to come will see a more effective use of resources to solve these problems, in particular:

- The use of different screening values between different countries for the international trading and trans-border monitoring of scrap metal;
- The lack of purpose-built facilities to dispose of the NORM waste which cannot be disposed of in landfill, mainly because nuclear waste disposal facilities are not designed to deal with the large volumes of wastes produced by some NORM industries;
- The environmental impact of unsustainable disposal options of very large volumes of NORM waste in some countries (phosphogypsum stacks in Florida for example);
- The impact of international conventions on the discharges and decommissioning of some NORM industries (oil and gas offshore installations for example);
- The identification of occurrences where occupational exposures might be unacceptable, especially in countries where occupational hygiene standards are not stringent enough or not properly enforced.

As far as Ireland is concerned, some work will be needed in the future to review the situation with regards to NORM. The RPII has identified specific areas which will have to

be examined. As with the problems identified by the international community and listed above, apart from a number of NORM items that have been detected in scrap in recent years, none of them has been identified as being of critical concern for Ireland.

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10 Glossary of Terms

Absorbed Dose
Quantity of energy imparted by the ionising radiation to unit mass of matter such as tissue. It is measured in grays (Gy). One Gy produces different biological effects on tissue depending on the type of radiation (alpha, beta or gamma).

Activity
Activity is a measure of the rate at which nuclear disintegration occurs. The unit of activity is the becquerel (Bq). One Bq is equivalent to one disintegration per second.

Collective Effective Dose
Total dose over a population group exposed to a given source. It is represented by the product of the average effective dose to the individuals in the group by the number of persons comprising the group. It is measured in man sieverts (manSv).

Committed Effective Dose
Total dose gradually delivered to an individual over a given period of time by the decay of a radionuclide following its intake into the body. The integration time is usually taken as 50 years for adults and 70 years for children.

Effective Dose
Weighted sum of the equivalent doses to the various organs and tissues. The weighting factor for each organ or tissue takes account of the fractional contribution of the risk of death or serious genetic defect from irradiation of that organ or tissue to the total risk from uniform irradiation of the whole body. The unit of effective dose is the sievert (Sv).

Equivalent Dose
The quantity obtained by multiplying the absorbed dose by a factor representing the different effectiveness of the various types of radiation in causing harm to tissues. It is measured in sieverts (Sv). One Sv produces the same biological effect irrespective of the type of the radiation.

Half-life
The time taken for the activity of a radionuclide to lose half its value by decay.

Radionuclide
An unstable nuclide that emits ionising radiation. The emissions may be either alpha, beta or gamma radiation.

Radiotoxicity
A measure of the dose per becquerel resulting from the ingestion of a particular radionuclide.

Appendix A

Amount of radioactivity discharged by the stack of the studied coal-fired power plant used to estimate the radiological impact of the atmospheric discharges.

Collecting the alpha and beta terms marked in the table below (symbols ¥ and ¶, respectively) and allowing for the polonium (Po) and lead (Pb) enhancements on the smaller emitted particles (factor 20 and 10, respectively), the activity emitted was calculated as follows:

Total alpha activity:

In the ^{232}Th series:
6 alpha → 6 x 53 Bq/kg
In the ^{238}U series – above radon:
4 alpha → 4 x 134 Bq/kg
In the ^{238}U series – below radon:
3 alpha, including ^{210}Po (enriched 20 times) → 2 x 92 + 1 x (92x20) Bq/kg
In the ^{235}U series:
7 alpha → 7 x 6 Bq/kg
In the ^{40}K series:
0 alpha

Therefore, total alpha = $6\times53+4\times134+2\times92+1\times(92\times20)+7\times6$ = 2920 Bq/kg of ash emitted

Total beta activity:

In the ^{232}Th series:
5 beta → 5 x 53 Bq/kg
In the ^{238}U series – above radon:
2 beta → 2 x 134 Bq/kg
In the ^{238}U series – below radon:
4 beta, including ^{210}Pb (enriched 10 times) → 3 x 92 + 1 x (92x10) Bq/kg
In the ^{235}U series:
5 beta → 5 x 6 Bq/kg
In the ^{40}K series:
1 beta → 1 x 650 Bq/kg

Therefore total beta = $5\times53+2\times134+3\times92+1\times(92\times10)+5\times6+1\times650$ = 2409 Bq/kg of ash emitted.

^{232}Th-series	^{238}U-series	^{235}U-series	^{40}K
¥ ^{232}Th ¶ ^{228}Ra ¶ ^{228}Ac } 53 ¥ ^{228}Th ¥ ^{224}Ra ¥ ^{220}Rn ¥ ^{216}Po ¶ ^{212}Pb } 51 ¶ ^{212}Bi ¥ ^{212}Po ¶ ^{208}Tl ^{208}Pb stable	¥ ^{238}U } 120 ¶ ^{234}Th ¶ ^{234}Pa ¥ ^{234}U ¥ ^{230}Th ¥ ^{226}Ra 134 ¥ ^{222}Rn ..... ¥ ^{218}Po ¶ ^{214}Pb ¶ ^{214}Bi 92 ¥ ^{214}Po ¶ ^{210}Pb 89 (92x10) ¶ ^{210}Bi ¥ ^{210}Po (92x20) ^{206}Pb stable	¥ ^{235}U } 6 § ¶ ^{231}Th ¥ ^{231}Pa ¶ ^{227}Ac ¥ ^{227}Th ¶ ^{223}Fr ¥ ^{223}Ra ¥ ^{219}Rn ¥ ^{215}Po ¶ ^{211}Pb ¥ ^{211}Bi ¶ ^{207}Tl ^{207}Pb stable	¶ ^{40}K } 650 ^{40}Ca

Single underlined: measured radionuclide and measured activity concentrations (in Bq/kg) in the coal fly ash [McAulay, 1986 and 1988], see Table 6.

Double underlined: radionuclide activity concentrations used in the ESB model (calculated on the basis of measurements by McAulay [1986 and 1988] plus 1.65 standard deviation, see Table 6, except for the U-235 series (§) for which the concentrations were estimated on the basis of the ratio of natural abundance of uranium isotopes ^{235}U / ^{238}U = 0.046.

¥ alpha emitters
¶ beta emitters

..... In the U-238 series, the dotted line symbolises the fact that elements above and below Rn-222 are considered to form two separate equilibrium series.

Tables

Table 1 Comparison of exclusion / exemption levels (Bq/kg) recommended by the EC and the IAEA for use in NORM industries

Radionuclide	EC (all types of NORM material)	EC (for wet sludge, from oil and gas industry only)	IAEA
U-238 sec (assumed to be in natural equilibrium with the U-235 chain) §	500	5,000	1,000
Ra-226+	500	5,000	
Pb-210+	5,000	100,000	
Po-210	5,000	100,000	
Th-232 sec	500	5,000	
Ra-228+	1,000	10,000	
Th-228+	500	5,000	
K-40	5,000	100,000	10,000

§ NORM processes do not cause a shifting of the natural isotope relation between U-238 and U-235. The dose contributions of these nuclides are considered in the results for the U-238 chain according to the natural isotope relation between U-328 and U-235. The specific activity of the nuclides of the U-235 chain amounts to 4.6% of the specific activity of the nuclides of the U-238 chain.

Table derived from: [European Commission, 2001a] [IAEA, 2004]. Nuclides for which the progeny is already accounted for in the dose calculations are marked with the sign "+"; when the equilibrium between nuclides of one decay chain is disturbed, the data on activity concentrations refer to the nuclide with the highest individual activity.

Table 2 **Specific activity concentrations of radionuclides from the U-238 and Th-232 series, K-40 and Cs-137 measured in peat, peat ash and ash pond effluent samples by gamma spectrometry.**

	U-238	Ra-226	Pb-210	Th-232	K-40
Minimum Detectable Limit MDL (in Bq/kg)	0.29	0.41	0.05	0.90	0.008
Raw peat (in Bq/kg)					
Arriving at plant	3.1±0.7	< MDL	21.6±2.8	< MDL	6.2±5.8
Arriving at plant	8.4±0.7	6.0±0.5	5.8±0.9	< MDL	< MDL
In tippler	12.3±2.9	3.6±0.6	31.4±3.6	< MDL	6.6±3.0
In bunker	8.5±1.8	1.6±0.3	43.5±5.3	< MDL	< MDL
Dust sampled in bunker	7.1±1.6	3.2±0.5	27.4±3.3	< MDL	< MDL
Average (rounded up)	8	4	26	1 (assumed)	7
Peat fly ash (in Bq/kg)	36.7±4.1	4.4±0.6	357.4±39.3	11.1±1.3	70.2±3.5
	166.6±10.2	46.6±3.7	469.9±52.6	< MDL	< MDL
Average (rounded up)	102	26	414	12 (max)	71 (max)
Peat bottom ash (in Bq/kg)	342.0±17.1	81.0±4.4	17.8±2.0	< MDL	7.9±0.9
	78.7±1.1	17.5±1.4	270.3±29.4	5.3±1.7	191.3±9.6
	50.4±3.9	11.9±1.0	214.2±22.8	3.5±1.1	125.1±6.3
	14.2±1.0	6.2±0.6	10.5±1.7	< MDL	< MDL
Average (rounded up)	122	30	129	5	109
Effluent ash pond (in Bq/l)	0.31±0.3	< MDL	7.4±1.0	< MDL	< MDL
	< MDL	0.7±0.4	0.66±0.49	< MDL	< MDL

Errors quoted are the counting uncertainties at one standard deviation from the mean count.

Table 3 Activity concentrations (Bq/kg) of radionuclides in other NORM materials and in Irish soils.

	U-238	Ra-226	Pb-210	Th-232	K-40
Raw peat - Finland (1)	16	11	30	6	28
Coal – UK average (2)	15	15	15	7.5	144
Peat fly ash – various Irish peat-fired plants (3)	133	71		7	32
	290	121		11	112
	74	68		14	263
	121	127		8	57
	38	31		10	153
Coal fly ash – UK average (2)	100	100	100-200	50	900
Irish soils - Average (4)		46		25	418
Peaty soils - Donegal (5)	79 (3-788)	104 (4-479)		35 (3-135)	526 (8-1088)
Other NORM materials					
Bauxite (6)		78		110	
Bauxite (7)	250			200	
Red mud (8)	260-540			340-500	
Red mud (9)		250		300	
Phosphate ore (7)	40-4800	30-4800		7-110	10-230
Phosphogypsum (10)		1000			
Zircon sands (7)	>500			>500	

Table derived from: (1) [Mustonen and Jantunen, 1985], (2) [Smith et al., 2001], (3) [Finch, 1998], (4) [Marsh, 1991], (5) [O'Dea and Dowdall, 1999], (6) [Von Philipshorn and Kuhna st, 1992], (7) [IAEA, 1996b], (8) [European Commission, 2001a], (9) [Hofmann *et al.*, 2000], (10) [O'Grady, 1992].

Table 4 **Maximum (with no respiratory protective equipment) effective dose from inhalation of airborne peat dust (total fraction) in the bunker area.**

Radionuclide r	Ra-226	Pb-210	Po-210	Ra-228	Th-228	Units
Activity concentration in the peat dust §	3.2	27.4	27.4	1	1	Bq/kg
Dust concentration ¥	25.6					mg/m^3
Ambient air activity concentration c_r ¶	8.2×10^{-5}	7.0×10^{-4}	7.0×10^{-4}	2.6×10^{-5}	2.6×10^{-5}	Bq/m^3
Inhalation dose factor $g_{inh,r}$ #	1.2×10^{-5}	1.1×10^{-6}	2.2×10^{-6}	1.7×10^{-6}	3.2×10^{-5}	Sv/Bq
$c_r \times g_{inh,r}$	9.8×10^{-10}	7.7×10^{-10}	1.5×10^{-9}	4.4×10^{-11}	8.2×10^{-10}	Sv/m^3
Total	4.2×10^{-9}					Sv/m^3
Exposure duration t_{exp}	100					h/y
Breathing rate B ‡	1.18					m^3/h
$t_{exp} \times B \times \sum (c_r \times g_{inh,r})$	0.5					µSv/y

§ See Table 2. Pb-210 and Po-210 are assumed to be in equilibrium; Ra-228 and Th-228 are assumed to be in equilibrium with Th-232.
¥ Dust concentration is equal to (A/V) where A is the amount of peat dust breathed in during an 8-h shift (23.78 mg) and V is the flow rate of the pump used for the experiment (2 l/min) multiplied by the duration of the experiment (465 min) and divided by 1000.
¶ Equals to the product of the activity concentration in the peat dust by the dust concentration.
# AMAD 5 µm [ICRP, 1994].
‡ [Smith *et al.*, 2001].

Table 5 **Summary of the occupational radiation doses calculated at the studied peat-fired power plant.**

Location and exposure duration	Dust inhalation (μSv)	External gamma radiation (μSv)	Total dose (rounded up) at given location for given exposure duration (μSv)
Tippler / 100 h/y	Undetermined	1.9	2.0
Bunker / 100 h/y	0.5	1.9	2.5
Boiler area / 680 h/y	Undetermined	19.8	20.0
Inactive bottom ash pile / 50 h/y	Undetermined	1.4	1.5
Active bottom ash pile / 500 h/y	Undetermined	14.5	14.5
Wet ash pond / 400 h/y	Undetermined	7.6	8.0
Maintenance duties / 170 h/y	Undetermined	Undetermined	undetermined
Total exposure = 2000 h/y	49 μSv/y		

Table 6 Activity concentrations (Bq/kg dry weight) of radionuclides measured in samples collected at the studied coal-fired power plant

	U-238	Ra-226	Pb-210	Th-232	K-40
Coal (1) – 16 samples	19 (5-45)	30 (6-67)		8 (2-13)	61 (20-100)
PFA					
(1) – 5 samples	120	134		53	650
(2) – 4 samples	116	118		69	545
This study – 5 samples		269 (172-317)	305 (254-387)	80 (40-107)	377 (191-625)
Bottom ash					
(1)– 2 samples	78	80 (60-100)		38 (29-47)	240 (180-300)
(2)– 4 samples	68 (48-91)	88 (73-94)		48 (39-61)	375 (310-460)
Boiler residues					
This study – 2 samples	163 (105-220)	73	366	62 (58-65)	374 (353-394)
Effluents (Bq/l)					
This study – 2 samples	< 2	< 4		< 1	8.5 (8.1-8.9)
Building materials (this study)					
Cement with PFA – 1 sample		123	502	25	273
Cement without PFA – 3 samples		107 (87-128)	1601 (963-1951)	15 (14-17)	232 (210-264)
Concrete with PFA – 1 sample		73	306	7	145
Concrete without PFA – 1 sample		62	766	9	205

¶ Maximum values + 1 standard deviation

Table derived from: (1) [McAulay, 1986 and 1988 - unpublished], (2) [AEA, 1993 - unpublished].

Table 7 Activity concentrations (Bq/kg) of radionuclides in coal and PFA as found in the literature

	U-238	Ra-226	Pb-210	Th-232	K-40
Coal					
UK (1)	15	15	15	7.5	144
Poland (2)	20-30	15-23	20-26	12-18	106-150
Brazil (3)	24-35	24-35	24-35	27-48	351-447
Belgium (4)		20		20	
World (5)	10-25	10-25	10-25	10-25	
World (6)	20	20	20	10	100
PFA					
UK (1) – emitted ash	79	57	188	29	
Poland (2) – trapped ash	38-185	54-119	43-264	47-264	448-758
Belgium (4) – emitted ash	700	700	2800	700	
Greece (7) – trapped ash (lignite)	964	904	1158	53	454
Romania (8) – trapped ash		114-121		77-97	617-729
Hungary (9) – trapped ash	1053-1519	1356-1470			
Australia (10) – trapped ash		96		170	203
World (5)	200-400	200-400	200-400	200	

Table derived from: (1) [Smith *et al.*, 2001], (2) [Bem *et al.*, 2002], (3) [Flues *et al.*, 2002], (4) [Zeevaert *et al.*, 2006], (5) [UNSCEAR, 2000], (6) [Corbett, 1983], (7) [Karangelos *et al.*, 2004], (8) [Pantelica *et al.*, 2001], (9) [Papp *et al.*, 2002], (10) [Beretka and Mathew, 1985].

Table 8 Annual effective dose from inhalation of radionuclides emitted by the stack of the studied power plant

	Inhalation dose for the studied power plant (μSv/y)	Inhalation dose in the UK [Smith *et al.*, 2001] (μSv/y) - for comparison purpose
U-238 *	$1.04 \cdot 10^{-2}$	$2.08 \cdot 10^{-2}$
Pb-210 ‡	$5.06 \cdot 10^{-3}$	$3.28 \cdot 10^{-3}$
Th-232 ¥	$7.91 \cdot 10^{-3}$	$2.59 \cdot 10^{-2}$
U-235 §	$2.35 \cdot 10^{-5}$	$2.59 \cdot 10^{-2}$
TOTAL	$2.34 \cdot 10^{-2}$	$7.58 \cdot 10^{-2}$

* Includes contributions from all members of the ^{238}U decay chain assumed to be in secular equilibrium.
‡ Includes contributions from ^{210}Pb and all daughters assumed to be in secular equilibrium.
¥ Includes contributions from all members of the ^{232}Th decay chain assumed to be in secular equilibrium.
§ Includes contributions from all members of the ^{235}U decay chain assumed to be in secular equilibrium.

Table derived from: Smith *et al.* [2001] Parameters used: exposure duration 8760 h/y; inhalation rate 0.83 m^3/h; fraction spent outdoor 0.1 and indoor 0.9; effective dose coefficients for inhalation of radionuclide for adult members of the public, default absorption types used [ICRP, 1996].

Table 9 Radon concentrations in the Irish natural gas extracted from the studied gas field - Grab sampling technique.

Measurement date	Concentration (Bq/m^3)
4/09/03	865
18/12/03	680
8/04/04	918
5/08/04	660
14/12/04	525
19/04/05	777
20/07/05	116
18/10/05	562

Table 10 Radon concentrations in the Irish natural gas extracted from the studied gas field – 3-month continuous measurements.

Measurement period	Concentration (Bq/m^3)
4/09/03 to 18/12/03	411
18/12/03 to 8/04/04	270
8/04/04 to 5/08/04	310
5/08/04 to 13/12/04	266
13/12/04 to 19/04/05	259
19/04/05 to 20/07/05	225
20/07/05 to 18/10/05	275

Table 11 Radon concentrations in the Irish natural gas extracted from the studied gas field – 8-month continuous measurements.

Measurement period	Concentration (Bq/m^3)
18/12/03 to 5/08/04	269
8/04/04 to 13/12/04	228
5/08/04 to 19/04/05	277
13/12/04 to 20/07/05	285

Table 12 Radionuclide activity concentrations (Bq/kg dry weight, unless specified) in the two sludge samples collected on the offshore platform (gas extraction industry).

Radionuclide	Sludge A	Sludge B
U-238	< 0.2	< 0.2
Ra-226	< 10	5.55±1.78
Pb-210	2900±65 (wet weight)	130±3 (wet weight)
Th-232	5.4±0.2	15.7±0.3
Ra-228	5.0±1.2	15.4±1.2
Th-228	10.1±0.2	5.4±0.2
K-40	18.8±4.3	22±3

Table 13 Radionuclide activity concentrations (Bq/kg dry weight) in samples collected in the bauxite refinery and comparison with other published data.

Reference and material	U-238 (maximum)	Th-232 (maximum)	U-235
This study			
Bauxite slurry	140	120	< 10
Scale top digester	250	260	20
Scale decanter	40	40	< 10
Red sand	150	170	7
Red mud	240	460	7
Liquid effluent (Bq/l)	3	0.3	< 10
[Von Philipsborn and Kühnast, 1992]			
Bauxite ore (Sierra Leone)Bauxite	30	30	
ore (Boké – Rep. Guinea)	130	160	
Bauxite ore (Queensland – Australia)	90	100	
Red mud (unspecified origin)	120	210	
[Beretka and Mathews, 1985]			
Red mud (Australia)	330	1130	
Red sand (Australia)	50	390	
[FNCA, 2005]			
Bauxite (Australia)	120	500	
Red mud (Australia)	400	1300	
[Cooper, 2005]			
Bauxite (Western Australia)	120-350	450-1050	
Red sand (Western Australia)	5-200	300-800	
Red mud (Western Australia)	150-600	1000-1900	
[European Commission, 2007]			
Red mud (Hungary)	250-570	260-400	7-11
Red mud (Bosnia and Herzegovina)	72	190	3
[European Commission, 2001a]			
Bauxite	50-500	50-500	
Red mud	260-540	340-500	
[Timmermans and van der Steen, 1996]			
Bauxite	500	400	
[IAEA, 2003]			
Bauxite	10-9000	35-1400	
Red mud	100-3000	100-3000	
[Marsh, 1991]			
Average in Irish soils	46	25	

Table 14 Range of doses to workers and members of the public from each of the four industries reviewed in this report.

	Workers	Members of the public
Peat-fired power production	• 50 μSv/y from all exposure pathways except maintenance duties not investigated • less than 300 μSv/y for workers involved in manufacture of building materials (concrete and cement) containing peat ash	• less than 300 μSv/y from exposure to building materials containing peat ash used in house construction • effluents would be exempted if peat-fired power production was considered a practice
Coal-fired power production	• less than 300 μSv/y from exposure to boiler residues when carrying out maintenance duties • less than 300 μSv/y for workers involved in manufacture of building materials (concrete and cement) containing coal ash • for other exposure scenarios, see NRPB report [Smith *et al.*, 2001]	• less than 300 μSv/y from exposure to building materials containing coal ash used in house construction • 20 nSv/y from atmospheric emissions through the stack (radon, total alpha and total beta) • effluents would be exempted if coal-fired power production was considered a practice
Natural gas extraction	• less than 100 μSv/y from exposure to sludge residues (maintenance duties) • no other significant exposures (all measurements below background)	• 8 μSv/y received by domestic gas users (from inhalation of radon contained in gas supplies)
Bauxite refining	• 300 to 600 μSv/y for workers involved in bauxite residue (red mud) management • no other significant exposures (all measurements below background)	• less than 300 μSv/y (from effluents and bauxite residue disposal area)

Figures

Figure 1 **Uranium 238 decay series.**

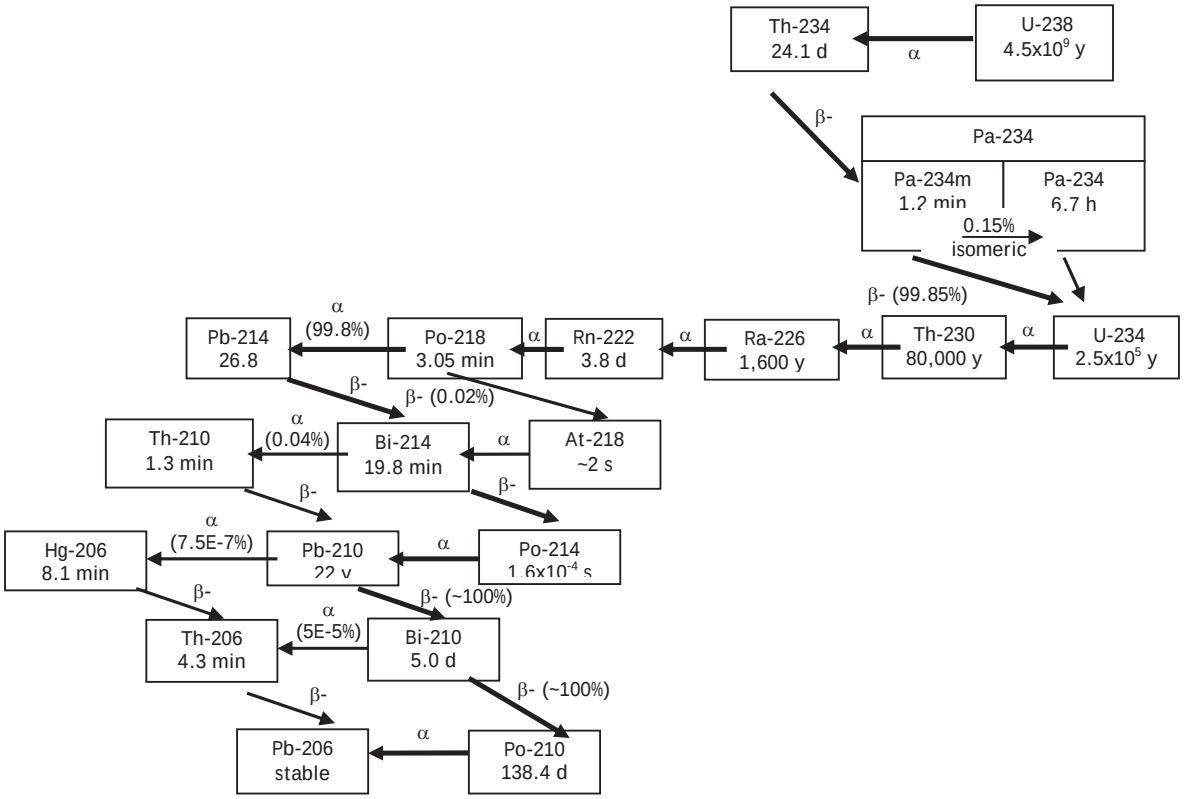


Figure 2 **Thorium 232 decay series.**

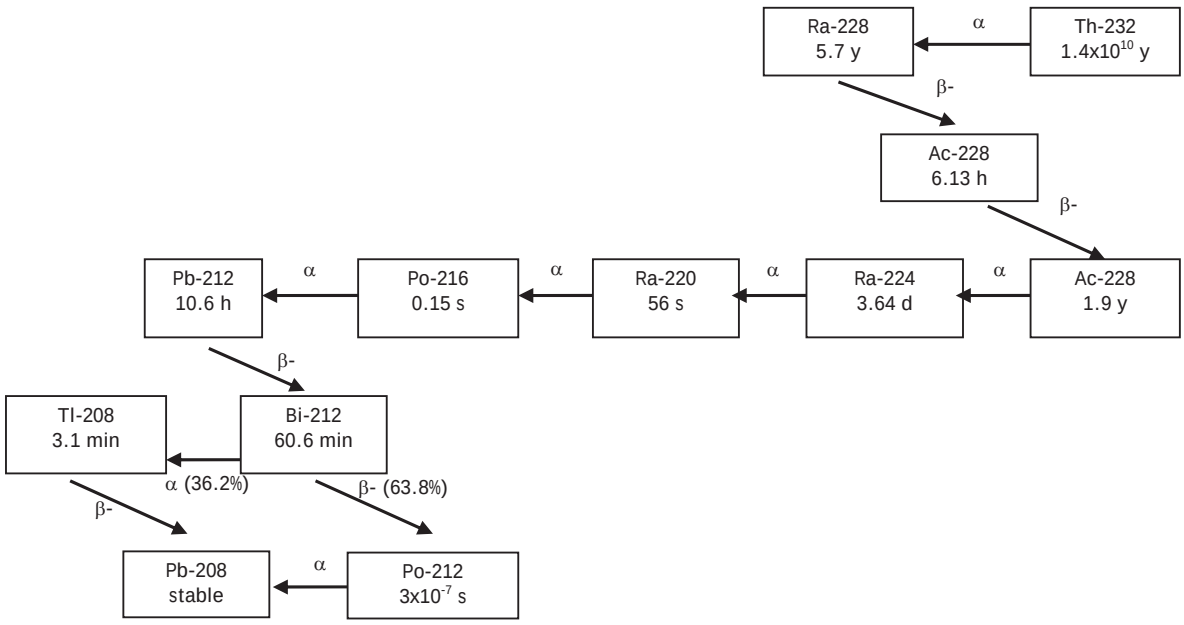
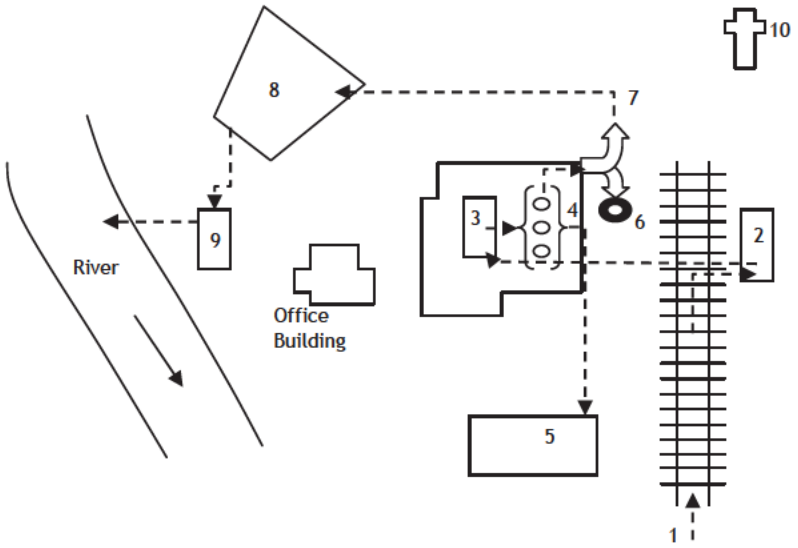


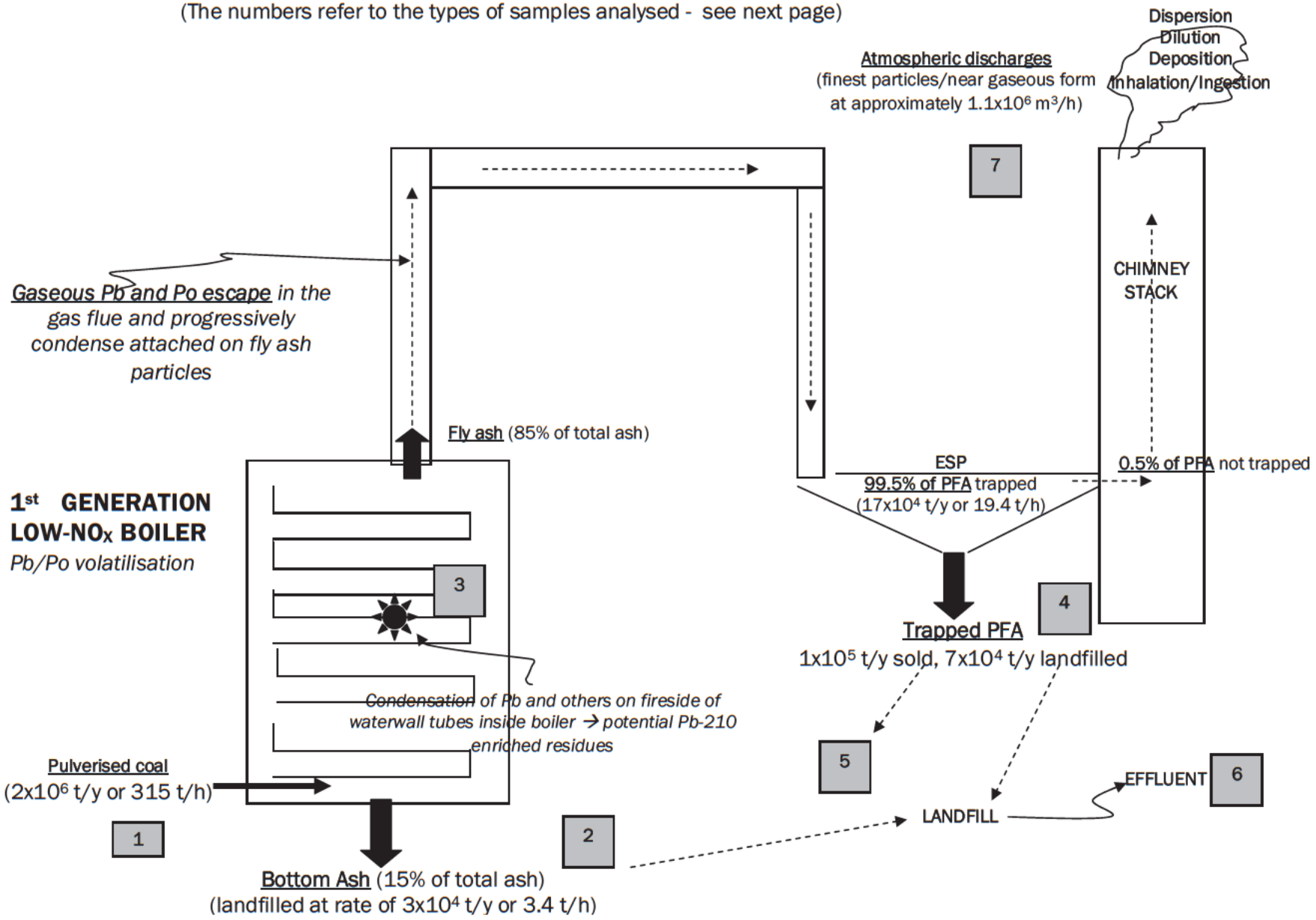
Figure 3 **Diagram of the studied peat-fired power plant with schematic locations of the measurements and samples.**



1. Incoming milled peat from the bog – two peat samples
2. Peat in tippler – one peat sample and one gamma dose rate measurement
3. Peat in bunker – two peat samples, two gamma dose rate measurements and one air sampling test
4. Boiler area - two gamma dose rate measurements
5. Dry bottom ash pile – four ash samples and two gamma dose rate measurements
6. Stack
7. Fly ash – two ash samples
8. Wet ash pond – one gamma dose rate measurement
9. Effluent from the ash pond – two samples
10. Control site (small church at the main entrance of the plant) – one gamma dose rate measurement

- - - - > peat and ash movement through the process

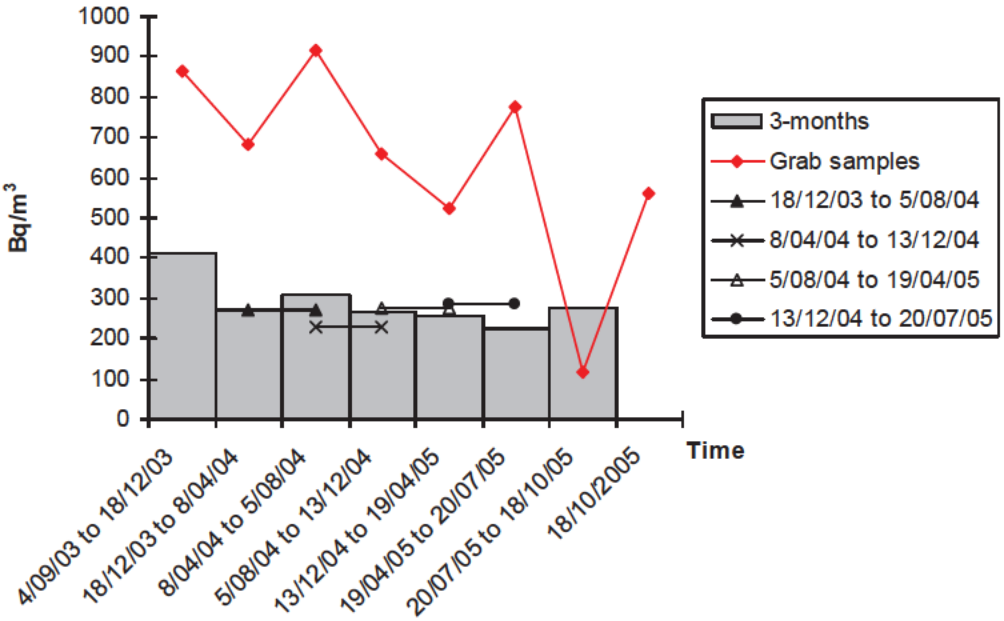
Figure 4 **Coal combustion cycle at the studied coal-fired power plant.**
(The numbers refer to the types of samples analysed - see next page)



Legend for Figure 4

1. pulverised coal samples – results from 1986 and 1988 unpublished data (16 samples)
2. bottom ash samples – results from 1986, 1988 and 1993 unpublished data (6 samples)
3. two samples of boiler residues – this study
4. PFA - results from 1986, 1988 and 1993 (unpublished data – 9 samples) and from this study (5 samples)
5. building materials: four samples of cement (one with, three without PFA) and two samples of concrete (one with, one without PFA) – this study
6. two samples of the runoff from the coal ash landfill – this study
7. atmospheric discharges – unpublished results from 1986-1990 model study

Figure 5 Radon levels measured in the Irish natural gas.





Radiological Protection Institute of Ireland

An Institiúid Éireannach um Chosaint Raideolaíoch

Mission Statement

In the three year period from 2008 to 2010 the RPII will grow the level of awareness and implementation of the measures needed to protect people in Ireland from the harmful effects of ionising (and non-ionising radiation) through scientifically based regulation, monitoring and advice.

Contact us

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Analysis of Solid Samples

Additional Assessment of Results

Client:	Aughinish Alumina Limited Askeaton Island Askeaton Co Limerick V94 V8F7 EIRE
Testing Facility:	SOCOTEC UK Unit 12, Moorbrook Southmead Industrial Park Didcot Oxfordshire OX11 7HP
Laboratory Reference:	21-0490-Supplement
Customer Reference:	Farmed Bauxite Residue Q3 2020 and Q4 2020
Quote Number:	ENR-ANU-10434
PO Number:	P4685681
Sample Received:	01 June 2021
Sample Condition:	Satisfactory, Ambient
Analysis Completed:	15 June 2021
Report Author:	
Author's Name:	Roger Benzing
Job Title:	Head of Nuclear Chemistry
Approved By:	
Approver's Name:	Charlene Hunston
Job Title:	Team Leader
Report Date:	08 July 2021

Sample Summary

Customer Reference	Laboratory Reference	Matrix	Sampling Date
Farmed Bauxite Residue Q3 2020	NA3281	Composite Sample (Bauxite Residue)	01/08/2020 12:00
Farmed Bauxite Residue Q4 2020	NA3282	Composite Sample (Bauxite Residue)	01/11/2020 12:00
Process Sand 2020	NA3283	Composite Sample (Bayer Process)	01/06/2020 12:00

Experimental

Gamma Spectrometry

ANU/SOP/2029 – The measurement technique is based on the use of high purity germanium (HPGe) detectors coupled to an Ortec gamma ray spectroscopy system. The gamma ray spectra are stored on a computer and analysed using the software programme Fitzpeaks for photopeak identification and quantification. The detectors are calibrated for efficiency using a mixed radionuclide standard, which covers an energy range of approximately 30-2000 keV. The efficiency of gamma rays between 30 keV and 120 keV are determined on an individual basis.

Application of decay corrections for the naturally occurring daughter radionuclides of uranium and thorium assumes that the series daughter radionuclides are all in secular equilibrium and therefore decay with the half-life of the first radionuclide in the series.

Deviating Sample Disclaimer

H) The sample matrices are not covered under UKAS accreditation schedule 1252 and are therefore not subject to our sample deviancy procedure.

Results

Results are presented in the following tables.

Any opinions and interpretations expressed herein are outside the scope of our UKAS accreditation.

The results in this test report relate only to the items tested, and test portions taken thereof. This test report must not be reproduced except in full, without written approval of the laboratory.

Supplementary information

Naturally Occurring Radioactive Material (NORM)

There are three main naturally occurring radioactive decay series present in soils and sediments and these are known as Naturally Occurring Radioactive Material (NORM). There is one thorium decay series headed by ^{232}Th and two uranium series; one headed by ^{235}U and the second ^{238}U (see Appendix 1). In nature, the radionuclides in these three decay series are approximately in a

state of secular equilibrium, in which the activities of all radionuclides within each series are nearly equal. The daughter radionuclides can therefore be used as estimators of other radionuclides in the decay chain.

Technologically Enhanced Naturally Occurring Radionuclide Material (TENORM)

When material containing NORM is processed this often concentrates the radioactivity of some daughter radionuclides and upsets the secular equilibrium therefore not all the daughter radionuclides will be equal. This material is often referred to as Technologically Enhanced Naturally Occurring Radionuclide Material (TENORM). We will indicate those radionuclides where equilibrium is not guaranteed.

Assessment of data

In the tables below, I have separated the radionuclides into the different decay series.

Uranium-238 series

Customer Reference	Laboratory Reference	Th-234 (Bq kg^{-1})	Pa-234m (Bq kg^{-1})	Ra-226 (Bq kg^{-1})	Bi-214 (Bq kg^{-1})	Pb-214 (Bq kg^{-1})	Pb-210 (Bq kg^{-1})
Farmed Bauxite Residue Q3 2020	**NA3281 ***	<83	<300	172 ± 47	72.4 ± 8.6	77.4 ± 8.1	<64
Farmed Bauxite Residue Q4 2020	**NA3282 ***	<77	<300	174 ± 47	84.2 ± 9.3	82.1 ± 8.4	<59
Process Sand 2020	**NA3283 ***	<85	<340	<56	47.1 ± 6.8	51.1 ± 6.1	<67

Thorium-234 is the direct daughter radionuclide of ^{238}U and is a good estimator of the activity of ^{238}U in this case all below the limit of detection.

The daughter radionuclides of ^{226}Ra in the series ^{214}Bi & ^{214}Pb can give a good estimate of the activity of ^{226}Ra but the immediate daughter of ^{226}Ra is ^{222}Rn which is a gas and thus it is possible for ^{214}Bi & ^{214}Pb to underestimate the ^{226}Ra activity. Radium-226 has only one gamma ray at 186 keV and the major gamma ray from ^{235}U also occurs at 186 keV, the reported ^{226}Ra is therefore usually overestimated but this activity can be used as an upper limit activity.

Uranium-235 series

Customer Reference	Laboratory Reference	U-235 (Bq kg^{-1})
Farmed Bauxite Residue Q3 2020	**NA3281 ***	<16
Farmed Bauxite Residue Q4 2020	**NA3282 ***	<16
Process Sand 2020	**NA3283 ***	<3.5

With the exception of ^{235}U itself, there are no significant gamma emitting radionuclides in the ^{235}U decay series.

Thorium-232 series

Customer Reference	Laboratory Reference	Ac-228 (Bq kg^{-1})	Ra-224 (Bq kg^{-1})	Pb-212 (Bq kg^{-1})	Bi-212 (Bq kg^{-1})	Tl-208 (Bq kg^{-1})
Farmed Bauxite Residue Q3 2020	**NA3281 ***	313 ± 26	251 ± 57	314 ± 26	350 ± 51	101.0 ± 8.9
Farmed Bauxite Residue Q4 2020	**NA3282 ***	304 ± 25	267 ± 59	312 ± 25	329 ± 48	105.0 ± 8.9
Process Sand 2020	**NA3283 ***	164 ± 15	120 ± 45	151 ± 14	160 ± 39	47.3 ± 5.2

The direct daughter of ^{232}Th is ^{228}Ra which does not produce any significant gamma ray emissions. We can estimate the activity of ^{228}Ra from the daughter radionuclide ^{228}Ac but the ^{228}Ra may not be in equilibrium with the ^{232}Th. Radium-224 is a good estimator of the activity of ^{228}Th. The immediate daughter of ^{224}Ra is ^{220}Rn which is a gas and thus it is possible for ^{212}Bi & ^{212}Pb to underestimate the ^{228}Ra activity however that is not the case for these samples. Bismuth-212 decays to two possible radionuclides with only a 35.9% probability to ^{208}Th and allowing for this it appears that there is reasonable equilibrium from ^{228}Ac through to ^{208}Th.

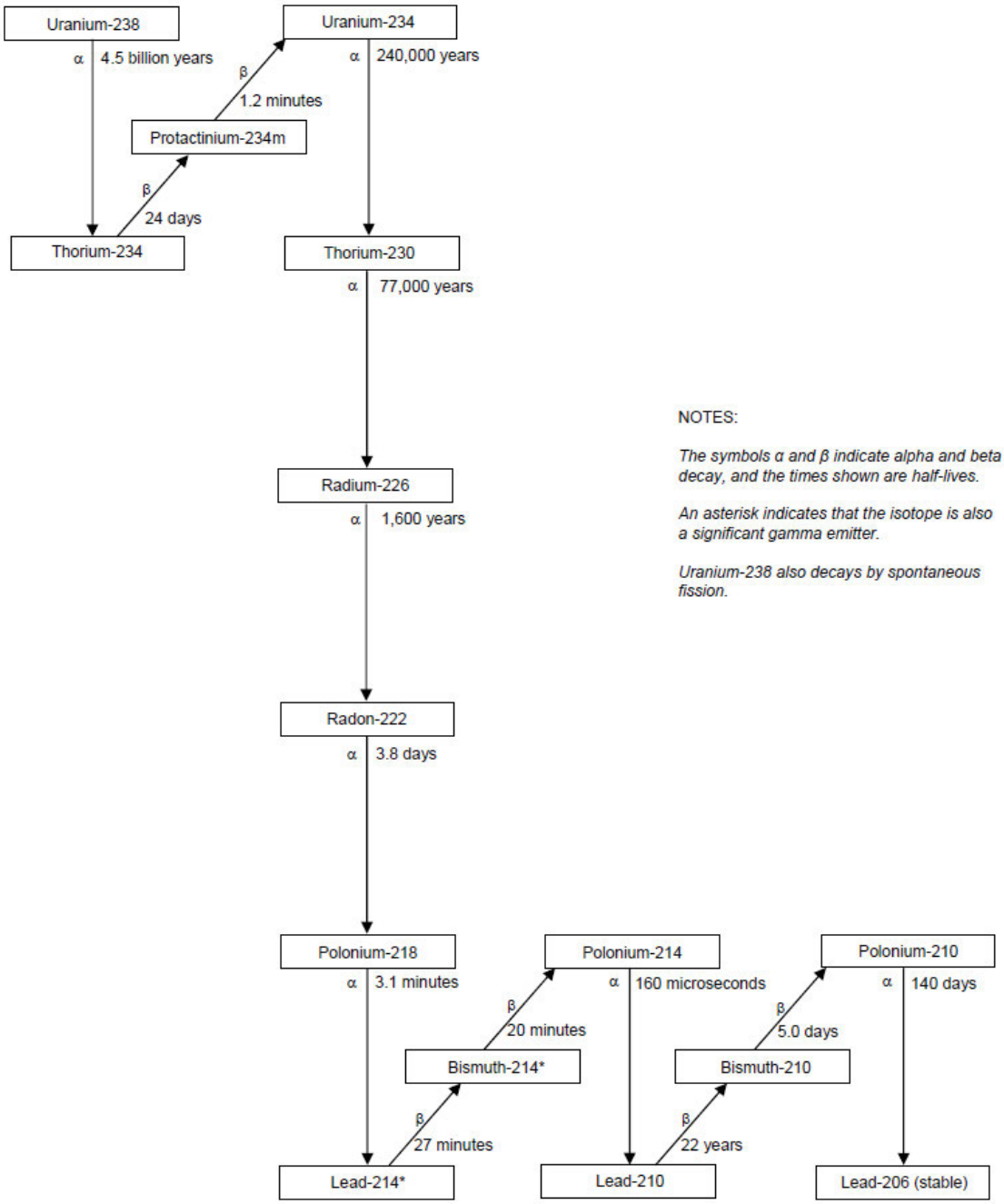
Table notes

1. Results are presented as Bq.kg^{-1} of sample as received and are decay corrected to the sampling date provided.
2. Analyses and/or samples marked with an asterisk are not UKAS accredited under schedule 1252.
3. Uncertainties are rounded to 2 significant figures; results are rounded to the same precision.
4. For results below the Limit of Detection, the LoD is rounded up to 2 significant figures.
5. Detector calibrations are based upon homogeneous standard solutions. For quantification purposes the sample is assumed to be homogeneous.

- End of Test Report –

Appendix 1

Uranium-238 decay series



NOTES:

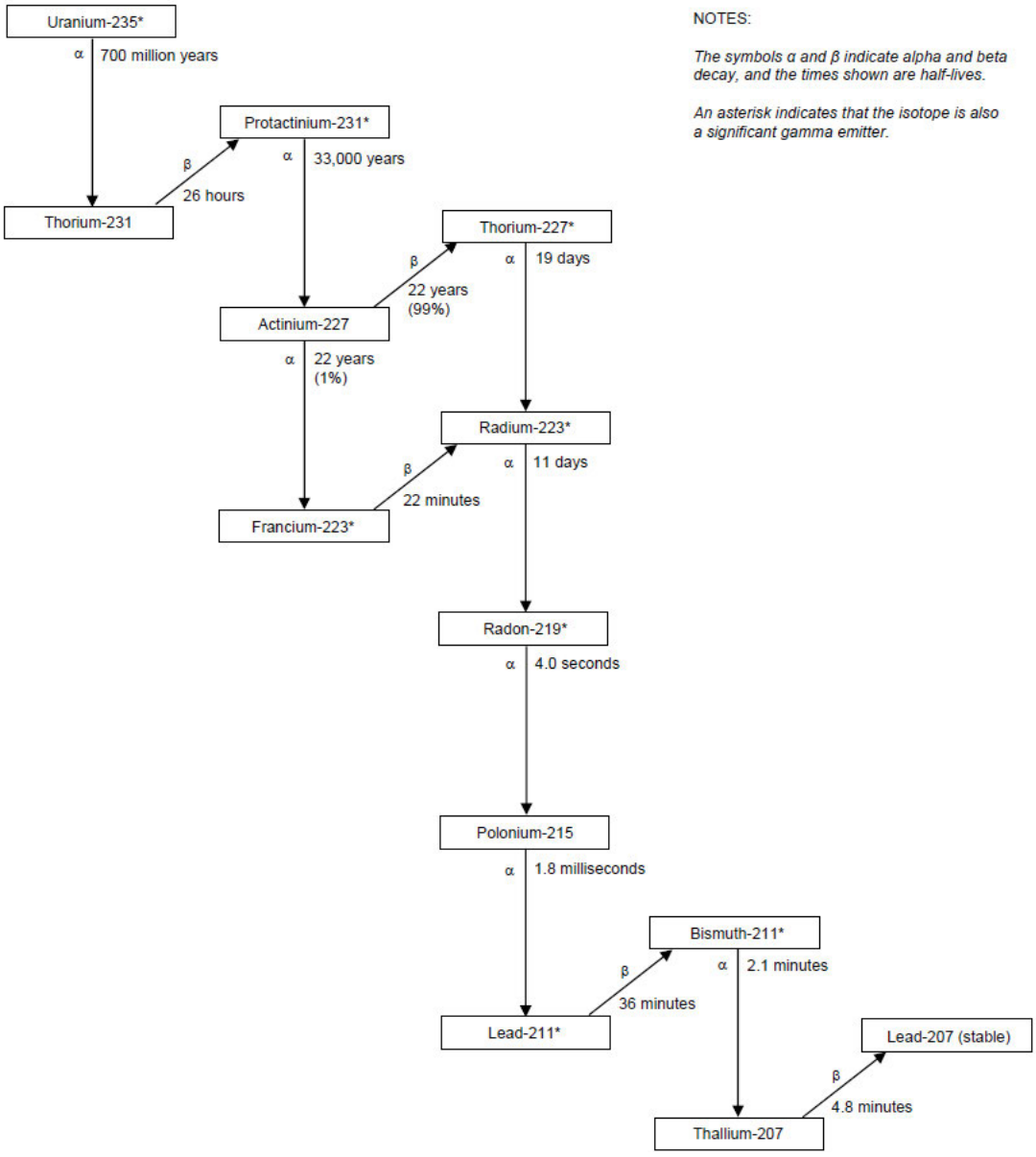
The symbols α and β indicate alpha and beta decay, and the times shown are half-lives.

An asterisk indicates that the isotope is also a significant gamma emitter.

Uranium-238 also decays by spontaneous fission.

SOCOTEC

Uranium-235 decay series



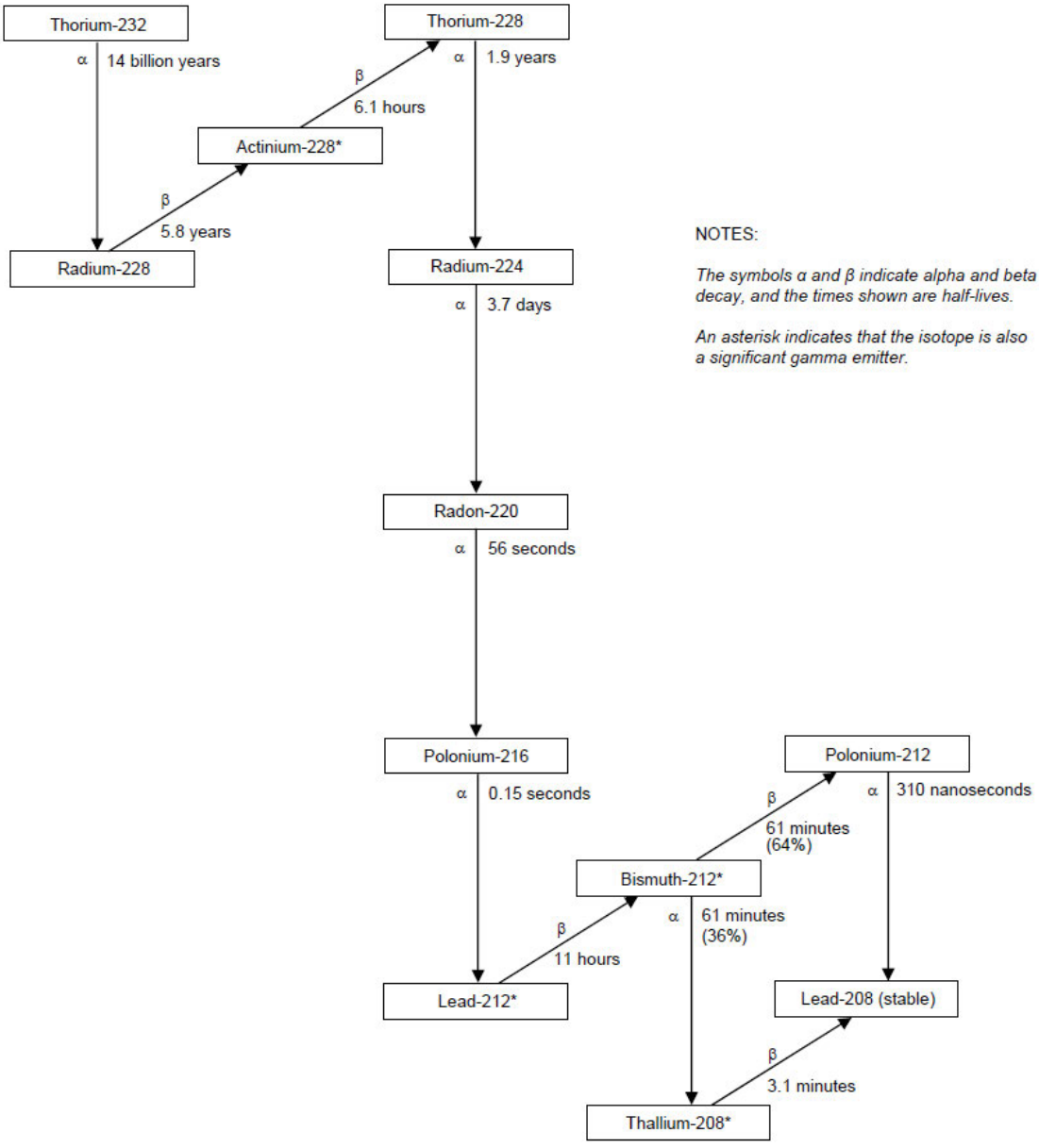
NOTES:

The symbols α and β indicate alpha and beta decay, and the times shown are half-lives.

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SOCOTEC

Thorium-232 decay series



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Analysis of Solid Samples

Additional Assessment of Results
Revision 1

Client:	Aughinish Alumina Limited Askeaton Island Askeaton Co Limerick V94 V8F7 EIRE
Testing Facility:	SOCOTEC UK Unit 12, Moorbrook Southmead Industrial Park Didcot Oxfordshire OX11 7HP
Laboratory Reference:	21-0490-Supplement-Rev1
Customer Reference:	Farmed Bauxite Residue Q3 2020 and Q4 2020
Quote Number:	ENR-ANU-10434
PO Number:	P4685681
Sample Received:	01 June 2021
Sample Condition:	Satisfactory, Ambient
Analysis Completed:	15 June 2021
Report Author:	
Author's Name:	Roger Benzing
Job Title:	Head of Nuclear Chemistry
Approved By:	
Approver's Name:	Jasper Hattink
Job Title:	Laboratory Manager
Report Date:	18 November 2021

Sample Summary

Customer Reference	Laboratory Reference	Matrix	Sampling Date
Farmed Bauxite Residue Q3 2020	NA3281	Composite Sample (Bauxite Residue)	01/08/2020 12:00
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The revision to this report is due to two typing errors on page four of the original 21-0490-Supplement report where reference was made to the radionuclide ^{208}Th which should have been ^{208}Tl. This has been amended in this revision of the report.

Supplementary information

Naturally Occurring Radioactive Material (NORM)

There are three main naturally occurring radioactive decay series present in soils and sediments and these are known as Naturally Occurring Radioactive Material (NORM). There is one thorium decay series headed by ^{232}Th and two uranium series; one headed by ^{235}U and the second ^{238}U (see Appendix 1). In nature, the radionuclides in these three decay series are approximately in a state of secular equilibrium, in which the activities of all radionuclides within each series are nearly equal. The daughter radionuclides can therefore be used as estimators of other radionuclides in the decay chain.

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Thorium-234 is the direct daughter radionuclide of ^{238}U and is a good estimator of the activity of ^{238}U in this case all below the limit of detection.

The daughter radionuclides of ^{226}Ra in the series ^{214}Bi & ^{214}Pb can give a good estimate of the activity of ^{226}Ra but the immediate daughter of ^{226}Ra is ^{222}Rn which is a gas and thus it is possible for ^{214}Bi & ^{214}Pb to underestimate the ^{226}Ra activity. Radium-226 has only one gamma ray at 186 keV and the major gamma ray from ^{235}U also occurs at 186 keV, the reported ^{226}Ra is therefore usually overestimated but this activity can be used as an upper limit activity.

Uranium-235 series

Customer Reference	Laboratory Reference	U-235 (Bq kg^{-1})
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Farmed Bauxite Residue Q4 2020	**NA3282 ***	<16
Process Sand 2020	**NA3283 ***	<3.5

With the exception of ^{235}U itself, there are no significant gamma emitting radionuclides in the ^{235}U decay series.

Thorium-232 series

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Farmed Bauxite Residue Q4 2020	**NA3282 ***	304 ± 25	267 ± 59	312 ± 25	329 ± 48	105.0 ± 8.9
Process Sand 2020	**NA3283 ***	164 ± 15	120 ± 45	151 ± 14	160 ± 39	47.3 ± 5.2

The direct daughter of ^{232}Th is ^{228}Ra which does not produce any significant gamma ray emissions. We can estimate the activity of ^{228}Ra from the daughter radionuclide ^{228}Ac but the ^{228}Ra may not be in equilibrium with the ^{232}Th. Radium-224 is a good estimator of the activity of ^{228}Th. The immediate daughter of ^{224}Ra is ^{220}Rn which is a gas and thus it is possible for ^{212}Bi & ^{212}Pb to underestimate the ^{228}Ra activity however that is not the case for these samples. Bismuth-212 decays to two possible radionuclides with only a 35.9% probability to ^{208}Tl and allowing for this it appears that there is reasonable equilibrium from ^{228}Ac through to ^{208}Tl.

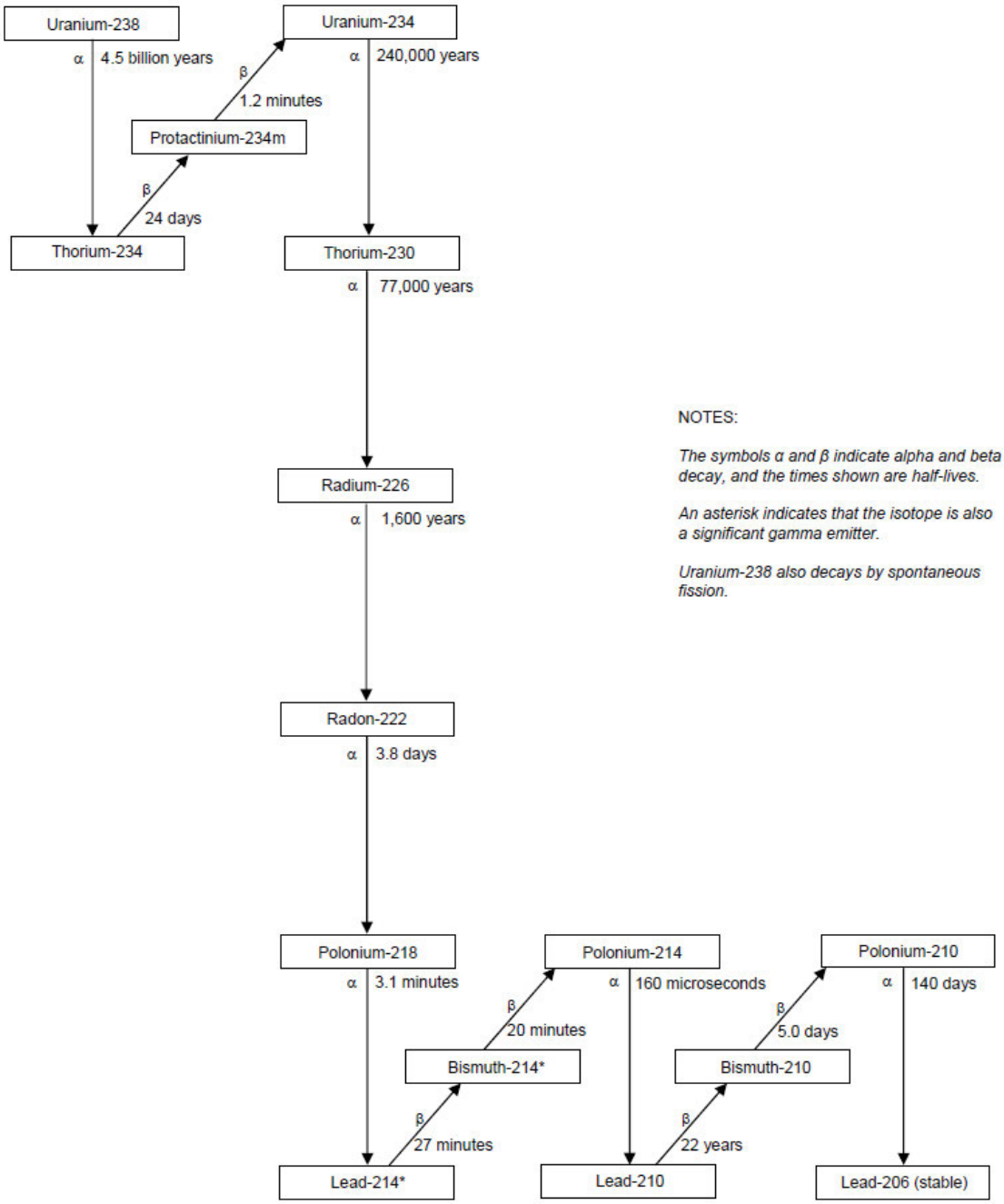
Table notes

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- End of Test Report –

Appendix 1

Uranium-238 decay series



NOTES:

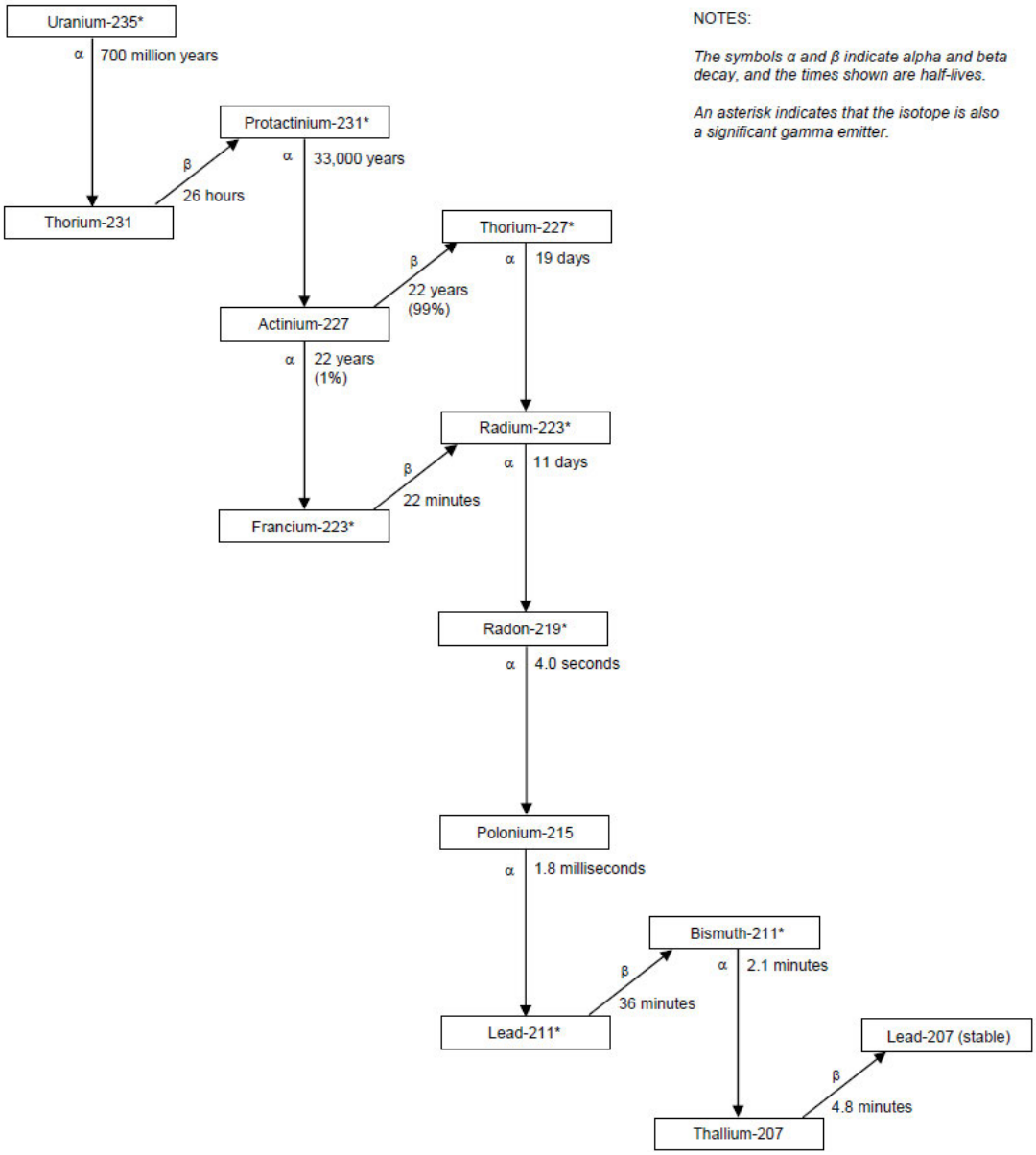
The symbols α and β indicate alpha and beta decay, and the times shown are half-lives.

An asterisk indicates that the isotope is also a significant gamma emitter.

Uranium-238 also decays by spontaneous fission.

SOCOTEC

Uranium-235 decay series



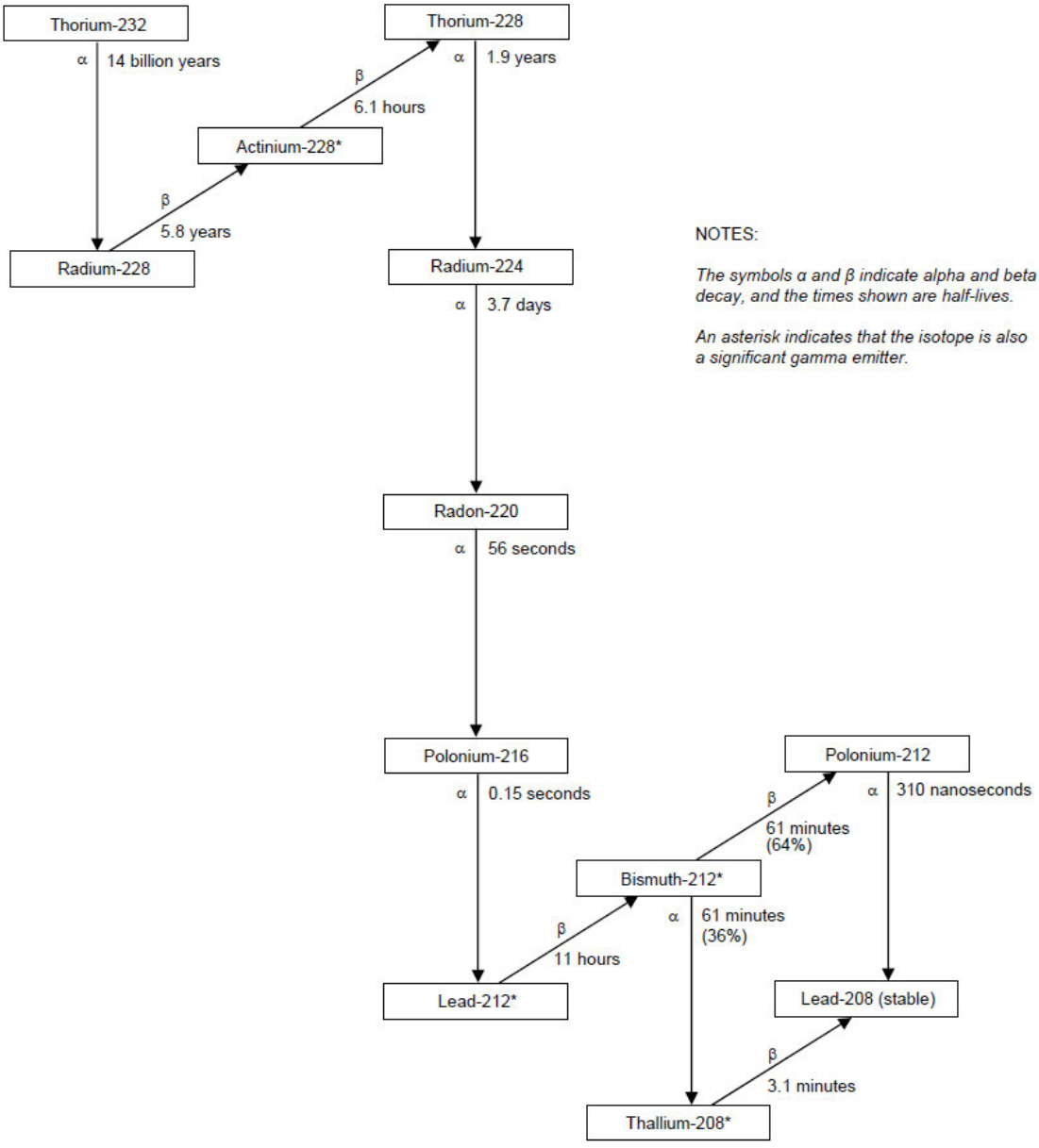
NOTES:

The symbols α and β indicate alpha and beta decay, and the times shown are half-lives.

An asterisk indicates that the isotope is also a significant gamma emitter.

SOCOTEC

Thorium-232 decay series



NOTES:

The symbols α and β indicate alpha and beta decay, and the times shown are half-lives.

An asterisk indicates that the isotope is also a significant gamma emitter.

APPENDIX

E TOXICITY PROFILES FOR CONSTITUENTS OF BAUXITE RESIDUE AND SALT CAKE

APPENDIX E: TOXICITY PROFILES FOR CONTAMINANTS OF POTENTIAL CONCERN

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E. INTRODUCTION

This appendix describes the toxicological review and methodology used in selecting inhalation exposure limits for the identified contaminants of potential concern (COPCs) that were carried forward for evaluation in the HHA. The selection of the COPCs are described in detail in Section 4.1 of the HHA and includes the following:

- Aluminium Goethite
- Aluminium Oxide
- Anatase and Rutile (Titanium Dioxide)
- Arsenic Trioxide
- Boehmite (Aluminium Oxide Hydroxide)
- Calcium Cancrinite
- Cerium Oxide
- Chromium Trioxide
- Copper Oxide
- Gallium Trioxide
- Gypsum (Calcium Sulfate Dihydrate)
- Hematite (Iron Oxide)
- Hydrogarnet
- Lead Oxide
- Manganese Oxide
- Niobium Pentoxide
- Perovskite (Calcium Titanium Trioxide)
- Sodium Fluoride
- Sodium Sulphate
- Sodium Oxalate
- Strontium Oxide
- Thorium Oxide
- Vanadium Pentoxide
- Yttrium Trioxide
- Zinc Oxide
- Zircon (Zirconium Silicate)

E.1. BACKGROUND

Exposure limits that are protective of human health are typically selected from TRVs published by appropriate regulatory agencies or, in cases where regulatory values are not available, a literature review is conducted, and published toxicity studies are reviewed and evaluated to derive a TRV. In this HHA, exposure limits are then compared against predicted COPC concentrations in ambient air (released from the Project) to estimate health risks associated with potential inhalation exposures.

Exposure limits that are protective of human health are derived based on the duration of exposure; long-term (chronic) and short-term (acute) durations. For this HHA, health-protective exposure limits for each COPC were selected to evaluate long-term (chronic) exposures representing repeated exposures over longer term periods that are conservatively assumed to take place over a lifetime.

Short-term (acute) exposures represent single or intermittent exposures lasting up to 24-hours. As presented in the toxicity profiles in **Section A2**, acute exposure limits are not available for identified COPCs (constituents of bauxite residue and saltcake). Acute exposures to Project-related emissions are associated with irritation of the upper respiratory airways and of the eyes based on the findings of the literature review (see **Section 4.1.1** and **Appendix A** of the HHA). Further, available literature reports that potential acute health effects are comparable to exposures to particulates in an urban setting. As such, this HHA evaluates potential acute health effects associated with bauxite residue and saltcake based on PM_{10} and $PM_{2.5}$ exposure limits**.**

E.2. OVERALL PROCESS FOR SELECTING EXPOSURE LIMITS

Exposure limits that are protective of human health were obtained from reputable regulatory agencies that regularly review and update the science supporting the exposure limits, provide supporting documentation, and/or engage a peer-review process in their standards development process. For the purposes of this HHA, these sources included:

- European Commission (EU) Air Quality Standards: https://ec.europa.eu/environment/air/quality/standards.htm;
- United Kingdom (UK) Air Quality Limits: https://uk-air.defra.gov.uk/air-pollution/uk-eu-limits;
- European Chemical Agency (ECHA) Evaluation, Authorisation and Restriction of Chemicals (REACH) Limits: https://echa.europa.eu/substances-restricted-under-reach;
- World Health Organization (WHO) Global Air Quality Guidelines: https://www.who.int/publications/i/item/9789240034228;
- California Ambient Air Quality Standards (CAAQS): https://ww2.arb.ca.gov/resources/california-ambient-air-quality-standards;
- Texas Commission on Environmental Quality (TCEQ) Effect Screening Levels (ESLs) and Air Monitoring Comparison Values (AMCVs): https://www.tceq.texas.gov/toxicology/amcv; and
- American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV-TWA): https://www.acgih.org/science/tlv-bei-guidelines.

Review of many regulatory agencies including the EU, UK, WHO and CAAQS identified that exposure limits are absent for the identified COPCs. Available health-protective exposure limits from the ECHA, TCEQ, and ACGIH are summarized for each COPC in **Section A2.**

Scientifically-defensible exposure limits applied in the HHA for each COPC were selected based on the following considerations:

- Established or derived by reputable and credible regulatory agencies;
- Derived based on human exposure studies;
- Year of primary study and toxicity review used to support exposure limit;
- Protective of public health based on the current scientific understanding of the health effects known and/or suspected to be associated with exposures to the COPC;
- Protective of sensitive individuals through the use of appropriate uncertainty factors; and,
- Supported by adequate documentation.

In the case that the above criteria were supported by more than one standard, guideline or objective, the most scientifically defensible limit was selected and the rationale for the decision is provided in the toxicity profiles

The following sections describe the chemical-specific toxicology, exposure limits and their basis, and the final exposure limit selection.

Toxicological information was summarized from the following sources where available:

- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles;
- American Conference of Governmental Industrial Hygienists (ACGIH) Supporting Documents for TLVs;
- European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Toxicological Summaries;
- National Center for Biotechnology Information - PubChem Compound Summaries; and

- Texas Commission on Environmental Quality (TCEQ) Development Support Documents.

E.3 CHEMICAL-SPECIFIC TOXICITY PROFILES

E.3.1 ALUMINIUM GOETHITE [$(FeAl)_2O_3 \cdot H_2O$; CAS#1310-14-1]

ACUTE TOXICITY / IRRITATION

There was no acute toxicity information identified for aluminium goethite.

Based on the ATSDR toxicological review, acute inhalation exposures to aluminium compounds may cause respiratory effects typically associated with inhalation of particulates and lung overload, including pulmonary toxicity, thickening of the alveolar walls and increases in absolute lung weights, as demonstrated in animal studies (ATSDR, 2008).

TCEQ identified an acute exposure limit for aluminium goethite based on meeting the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM). This is because for species of limited concern, the determination of the individual species impacts are not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

CHRONIC TOXICITY

There was no chronic toxicity information identified for aluminium goethite.

Based on the ATSDR toxicological review, chronic inhalation exposures to aluminium compounds may cause respiratory effects, including increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight. The lung effects observed in humans and animals are suggestive of dust overload. Subtle neurological effects have also been observed in workers chronically exposed to aluminium dust or fumes. These effects include impaired performance on neurobehavioral tests (ATSDR, 2008).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	SOURCE
ECHA	-	-	-	-
ACGIH	**1 mg/m^3**	**Respiratory and neurological effects**	**Chronic - human (Sjogren & Elinder, 1992)**	**ACGIH (2008)** *Surrogated to aluminium metal and insoluble compounds*
TCEQ	Must meet NAAQS		-	TCEQ (2021) *Surrogated to PM*

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH established a TLV-TWA of 1 mg/m^3 for aluminium and its insoluble compounds (including aluminium oxide and aluminium in bauxite ore dust). The authors reviewed

	available literature and concluded that a urinary aluminium level of 100 µg/L (corresponding to an airborne concentration of 1.6 mg/m^3) was a critical concentration for development of neurological effects based on an occupational study by Sjogren and Elinder (1992). The study identified that long-term exposures to aluminium and aluminium compounds leading to body burdens equivalent to breathing 1.6 mg/m^3 for 40 years can result in an increased prevalence of neurological effects (ACGIH, 2008). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ identified a chronic exposure limit for aluminium goethite based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for aluminium goethite.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for aluminium goethite.
CARCINOGENICITY	There was no carcinogenicity information identified for aluminium goethite.
SENSITIVE SUBPOPULATIONS	Children are not more sensitive to aluminium exposures, and developmental effects from aluminium have not been seen in animals unless exposed to large amounts (ATSDR, 2008).
SELECTED EXPOSURE LIMIT	The ACGIH limit for aluminium metal and insoluble compounds is selected for aluminium goethite since the TCEQ limit is surrogated to PM and not based on the toxicity of the COPC. Aluminium goethite is an insoluble aluminium compound; therefore, the ACGIH limit is an appropriate surrogate. An additional uncertainty factor of 100 was applied to the ACGIH limit to account for sensitive individuals including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of **0.01 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2008. Toxicological Profile for Aluminium. American Conference of Governmental Industrial Hygienists (ACGIH). 2008. Aluminium Metal and Insoluble Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Aluminium Goethite. Accessed online at: https://echa.europa.eu/substance-information/-/substanceinfo/100.013.797. Last accessed in October 2021. National Center for Biotechnology Information. 2021. PubChem Compound Summary for CID 91502, Goethite (Fe(OH)O). Retrieved October 7, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/Goethite-_Fe_OH_O. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021.

E.3.2 ALUMINIUM OXIDE [Al_2O_3; CAS#1344-28-1]

ACUTE TOXICITY / IRRITATION

Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals following acute exposures to aluminium compounds, including pulmonary toxicity, thickening of the alveolar walls and increases in absolute lung weights (ATSDR, 2008).

TCEQ identified an acute exposure limit for aluminium oxide based on meeting the National Ambient Air Quality Standards (NAAQS) for PM. This is because for species of limited concern, the determination of the individual species impacts are not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

CHRONIC TOXICITY

Chronic inhalation exposures to aluminium compounds have been shown to cause respiratory effects, including increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight. The lung effects observed in humans and animals are suggestive of dust overload. Subtle neurological effects have also been observed in workers chronically exposed to aluminium dust or fumes. These effects include impaired performance on neurobehavioral tests (ATSDR, 2008).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	3 mg/m^3 (worker) 0.75 mg/ m^3 (general public)	Pulmonary toxic effects	Chronic – animal (Gross *et al.*, 1973)	$UF_A = 2.5$ $UF_H = 5$ (workers) $UF_A = 2.5$ $UF_H = 10$ (public)	ECHA (2021)
ACGIH	**1 mg/m^3**	**Respiratory and neurological effects**	**Chronic - human (Sjogren & Elinder, 1992)**		**ACGIH (2008)**
TCEQ	Must meet NAAQS		-	-	TCEQ (2021) *Surrogated to PM*

Notes:

Bold = selected limit

UF = uncertainty factor; UFH (for intraspecies human uncertainty); UFA (for animal to human uncertainty); UFsub (for subchronic to chronic uncertainty); UFL (for LOAEL to NOAEL uncertainty); UFD (for incomplete database uncertainty)

European Chemical Agency (ECHA)

ECHA listed a chronic inhalation limit for aluminium oxide based for workers of 3 mg/m^3 and for the general public of 0.75 mg/m^3. These limits were established based on Gross *et al.* (1973), an animal study that exposed 30 rats to aluminium oxide dust (0.8 µm in size) within

	chambers for 6 months at a dose of 75 mg/m^3 and for 12 months at a dose of 30 mg/m^3 for 6 hours per day, 5 days per week. A follow-up examination occurred 30 months after exposure. Effects observed included dust-filled macrophages; no alveolar proteinosis, endogenous lipid pneumonitis or fibrosis. Aluminium oxide was determined to act as a low cytotoxic, poorly soluble particulates (PSPs) causing pulmonary toxic effects, where the effects after inhalation are attributable to the particle rather than a substance specific toxicity. A NOAEL of 75 mg/m^3 from this study was selected as the point of departure (POD) based on respiratory and neurological effects. For the workers exposure limit, the NOAEL was adjusted for an 8-hr exposure day, for differences in respiratory rates, and for differences in experimental and human exposure conditions. An uncertainty factor of 2.5 was applied for interspecies differences and 5 for intraspecies differences. For the general population exposure limit, the NOAEL was adjusted for continuous exposure and differences in experimental and human exposure conditions. An uncertainty factor of 2.5 was applied for interspecies differences and 10 for intraspecies differences (ECHA, 2021). ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH established a TLV-TWA-TWA of 1 mg/m^3 for aluminium and its insoluble compounds. The authors reviewed available literature and concluded that a urinary aluminium level of 100 µg/L (corresponding to an airborne concentration of 1.6 mg/m^3) was a critical concentration for development of neurological effects based on an occupational study by Sjogren and Elinder (1992). The study identified that long-term exposures to aluminium and aluminium compounds leading to body burdens equivalent to breathing 1.6 mg/m^3 for 40 years can result in an increased prevalence of neurological effects (ACGIH, 2008). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ identified a chronic exposure limit for aluminium oxide based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	Aluminium oxide is not considered genotoxic based on the bacterial reverse mutation assay and an in vitro gene mutation study in mammalian cells. Cytogenicity/chromosome aberration was observed in mammalian cells (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There is a lack of epidemiological and animal studies related to developmental toxicity from inhalation of aluminium oxide, aluminium hydroxide and aluminium metal. Reproductive toxicity may be inferred from oral exposure studies as reproductive toxicity is a result of systemic effects. Animal studies based on oral exposures have not shown evidence of developmental effects in both males and females (ECHA, 2021).
CARCINOGENICITY	ECHA concluded that the current weight of evidence does not support respiratory carcinogenic effects from inhalation exposure to aluminium metal/aluminium oxide, or systemic carcinogenic effects from exposure to aluminium metal and aluminium oxide (ECHA, 2021). Aluminium metal and its insoluble compounds are not classifiable as a human carcinogen (PubChem, 2021)
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for Aluminium Oxide from ECHA, PubChem or TCEQ. Children are not more sensitive to aluminium exposures, and developmental effects have not been seen in animals unless exposed to large amounts (ATSDR, 2008).

SELECTED EXPOSURE LIMIT	The ACGIH limit is selected for aluminium oxide since it is based on chronic exposure to humans. The TCEQ ESL is surrogated to PM and not based on the toxicity of COPC and the ECHA REACH limit is based on an older animal study. An additional uncertainty factor of 100 was applied to the ACGIH limit to account for sensitive individual including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of **0.01 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2008. Toxicological Profile for Aluminium. American Conference of Governmental Industrial Hygienists (ACGIH). 2008. Aluminium Metal and Insoluble Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Aluminium Oxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/16039/7/1. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. 2021.. PubChem Compound Summary for CID 9989226, Aluminium oxide. Accessed online at: https://pubchem.ncbi.nlm.nih.gov/compound/Aluminium-oxide. Last updated in October 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021.

E.3.3 ANATASE AND RUTILE [TiO_2; CAS#13463-67-7]

**Also known as Titanium Dioxide*

ACUTE TOXICITY / IRRITATION	Based on a toxicological review by ACGIH, acute intraperitoneal exposures to titanium dioxide in animals have shown it to be an inert dust (showing a tendency to remain in the tissue but not cause a proliferative response) (ACGIH, 2001). Titanium dioxide has been tested in various *in vivo* skin and eye irritation studies. All tests show a negative response; thus, titanium dioxide does not require classification either as skin or as eye irritant (ECHA, 2021). TCEQ adopted the short-term ESL for a one hour exposure period of 50 µg/m^3 from the OSHA 8 hr TWA for titanium dioxide of 5 mg/m^3 with a safety factor of 100 (TCEQ, 2021).
CHRONIC TOXICITY	Based on a toxicological review by ACGIH, chronic inhalation exposures to titanium dioxide in animals have shown pulmonary irritation. There is lack of conclusive evidence to support a relationship between occupational exposure to titanium dioxide and pulmonary fibrosis, cancer or other adverse health effects (ACGIH, 2001).

Based on the ECHA review, titanium dioxide showed adverse pulmonary effects in chronic inhalation studies in animals only at concentrations above the maximum tolerated dose (ECHA, 2021).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	SOURCE
ECHA	-	-	-	ECHA (2021)
ACGIH	**10 mg/m^3**	**Respiratory irritation**	**Chronic animal (Lee *et al.*, 1986)**	**ACGIH (2001)**
TCEQ	0.005 mg/m^3	Adopted from OSHA	-	TCEQ (2021)

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH derived a TLV-TWA of 10 mg/m^3 for titanium dioxide. The TLV-TWA was based on Lee *et al.* (1986), who conducted a 2-yr inhalation study on rats exposed to titanium dioxide at concentrations of 0, 10, 50, or 250 mg/m^3 for 6 hrs/day, 5 days/week. Squamous cell carcinomas developed following exposure to 250 mg/m^3 for the full 2 years. At 50 mg/m^3, massive accumulations of macrophages and foamy dust cells were reported which were indicative of pulmonary air-space overload. At 10 mg/m^3, a particulate (insoluble) not otherwise specified (PNOS) response was observed, whereby the architecture of the air spaces were unchanged, there was no significant formation of scar tissue, and the tissue reaction was potentially revisable. The TLV-TWA of 10 mg/m^3 is intended to protect against respiratory tract irritation, and potential overload of pulmonary air-space architecture and normal clearance mechanisms (ACGIH, 2001).

Texas Commission on Environmental Quality (TCEQ)

TCEQ adopted the long-term ESL of 5 µg/m^3 from the OSHA 8 hr TWA for titanium dioxide of 5 mg/m^3 with a safety factor of 1000 (TCEQ, 2021).

GENOTOXICITY / MUTAGENICITY	Titanium dioxide has been tested in bacterial reverse mutation assays, in vitro gene mutation and clastogenicity tests as well as *in vivo*. All tests show a negative response; thus, titanium dioxide does not require classification for mutagenic properties (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for anatase and rutile or titanium dioxide.
CARCINOGENICITY	Titanium dioxide is not classifiable as a human carcinogen (PubChem, 2021).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for anatase and rutile or titatium dioxide.

SELECTED EXPOSURE LIMIT	The ACGIH limit is selected for anatase and rutile given that the TCEQ ESL is adopted from OSHA with no further background information on its derivation. An additional uncertainty factor of 1000 was applied to the ACGIH limit to account for uncertainties related to animal to human, consideration of sensitive individuals including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of 0.01 mg/m^3 is applied in the quantitative risk analysis.
REFERENCES*	American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Titanium Dioxide. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Titanium dioxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15560/7/10/2. Last updated July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 26042, Titanium dioxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Titanium-dioxide. Last updated in October 2021. Last accessed in October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Titanium dioxide was not listed under ATSDR.*

E.3.4 ARSENIC TRIOXIDE [AS_2O_3; CAS#1327-53-3]

ACUTE TOXICITY / IRRITATION	A toxicological review by ATSDR concluded that breathing high levels of inorganic arsenic can cause a sore throat or irritated lungs (ATSDR, 2007). TCEQ developed an acute (1 hr) AMCV of 13 $\mu g/m^3$ for arsenic trioxide based on studies with inorganic arsenic compounds (TCEQ, 2012). The AMCV was derived from Holson *et al.* (1999), an animal study where female rats were exposed to whole body inhalation of arsenic trioxide dust at 0, 0.3, 3, and 10 mg/m^3 for 6 hr beginning 14 days prior to mating with additional 6 hr/day exposure through mating and gestation, until gestational day 19. . The NOEAC of 3000 $\mu g/m^3$ based on maternal toxicity in rats (shown as rales during pre-mating and gestation exposure) was selected as the point of departure (POD). TCEQ used the single day of exposure (i.e., 6 hrs) from the experimental study as the exposure duration because the reproductive/developmental effects may have been caused by only a single day's exposure that occurred at a critical time during gestation. The POD was adjusted for a 1 hr exposure concentration and a human equivalent concentration. An uncertainty factor of 3 was applied for interspecies extrapolation, an UF of 10 for intraspecies variability, and an UF of 10 for database uncertainty to account for the lack of acute human studies and the limited number of animal studies relevant to the short-term inhalation exposure scenarios. The AMCV was used to derive an ESL of 3 $\mu g/m^3$ based on a target hazard quotient of 0.3 (TCEQ, 2013).
CHRONIC TOXICITY	A toxicological review by ATSDR concluded that workers exposed to inorganic arsenic through inhalation experience irritation to the mucous membranes of the nose and throat, which may

lead to laryngitis, bronchitis or rhinitis. Very high exposures to workers can also cause perforation of the nasal septum. However, no studies have found a conclusive relationship between inhaled inorganic arsenic and respiratory disease. There is some evidence that inhaled inorganic arsenic can produce cardiovascular effects in humans, but these effects are better characterized from oral exposures. Occupational exposure studies have shown peripheral neurological effects in workers associated with arsenic trioxide exposure; however, the exposure levels were difficult to quantify (ATSDR, 2007).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	0.005 mg/m^3 (workers) 0.0025 mg/m^3 (general public)	Carcinogenicity	Chronic (oral) –human (Ahsan *et al*., 2006)	$UF_D = 3$	ECHA (2021)
ACGIH	0.01 mg/m^3	Upper respiratory tract; skin, liver, peripheral vasculature; lung cancer	Chronic – human (Pinto *et al*, 1978; Enterline, 1982 and 1987)	TLV-TWA was converted from 0.2 mg/m^3 to 0.01 mg/m^3 to account for uncertainty	ACGIH (2001)
TCEQ	**0.000067 mg/m^3 ***	**Respiratory and lung cancer**	**Chronic - human (Lubin *et al*., 2008)**	-	**TCEQ (2013)**

Notes:

Bold = selected limit

* The resulting air concentration at 1 in 100,000 excess lung cancer risk based on the final URF of 1.5E-04 per µg/m^3

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

European Chemical Agency (ECHA)

ECHA derived chronic exposure limits for arsenic trioxide of 5 µg/m^3 for workers and 2.5 µg/m^3 for the general public based on a chronic drinking water exposure study in humans (ECHA, 2021).

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH derived a TLV-TWA-TWA of 0.01 mg/m^3 for arsenic and its inorganic compounds including arsenic trioxide. The TLV-TWA was derived from a mortality study involving 2800 workers at a copper smelter (Pinto *et al*, 1978; Enterline PE, 1982, 1987), where a positive relationship between time-weighted exposure to arsenic and risk of lung cancer was identified. Workers in the lowest exposure category (0.2 mg/m^3) exhibited an elevated excess risk of respiratory cancer, which was selected as the point of departure (POD). To allow some measure of safety and to account for uncertainty, a TLV-TWA-TWA of 0.01 mg/m^3 was recommended. This TLV-TWA is intended to protect against effects on upper respiratory tract, skin, liver, peripheral vasculature, as well as lung cancer. (ACGIH, 2001).

	Texas Commission on Environmental Quality (TCEQ) TCEQ developed a long-term ESL/AMCV of 0.000067 mg/m^3 for inorganic arsenic including arsenic trioxide based on lung cancer mortality rates associated with inhalation of inorganic arsenic compounds. The ESL was derived from Lubin *et al*. (2008), an occupational study looking at excess lung cancer mortality for all workers adjusting for year of hire. The study used Texas-specific mortality rates for 2001-2005 from lung cancer and Texas-specific survival rates for 2005. Texas air concentrations corresponding to an excess cancer risk of 1 in 100,000 based on the final URF of 1.5E-04 per µg/m^3 was selected as the ESL/AMCV (TCEQ, 2013).
GENOTOXICITY / MUTAGENICITY	A toxicological review by ATSDR concluded that inorganic arsenic compounds are not directly mutagenic. There is evidence that inorganic arsenic can cause indirect DNA damage, including chromosomal aberrations, micronucleus formation and sister chromatid exchanges in vitro and *in vivo*; however, this occurred at high concentrations, above those that humans would be exposed to systemically (ATSDR, 2007)
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	A toxicological review by ATSDR found some evidence that long-term exposure to arsenic in children may result in lower IQ scores, that exposure to arsenic in the womb and early childhood may increase mortality in young adults, and that inhaled or ingested arsenic may harm pregnant women or the fetus. Studies in animals show that large doses of arsenic that causes illness in pregnant females, can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues (ATSDR, 2007)
CARCINOGENICITY	Inorganic arsenic is classified as a confirmed human carcinogen (ACGIH, 2001). A toxicological review by ATSDR concluded that several occupation studies looking at inhalation exposures to arsenic trioxide dust at copper smelters have found an association between inhalation exposure to arsenic and lung cancer (ATSDR, 2007).
SENSITIVE SUBPOPULATIONS	There is some evidence that arsenic may cause developmental effects to unborn fetuses and children (ATSDR, 2007).
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.000067 mg/m^3** is selected for inorganic arsenic including arsenic trioxide given that the limit is based on the most recent study and is protective of the general population. This exposure limit protects against lung cancer mortality and represents an air concentration that correspond to an excess cancer risk of 1 in 100,000 based on the final URF of 1.5E-04 per µg/m^3. The ECHA REACH limit is not further considered as it is based on route-to-route extrapolation rather than direct exposure to arsenic particulates through inhalation.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological Profile for Arsenic (Update). Atlanta, GA: U.S. Department of Health and Human Services. Public Health Service.

	American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Arsenic and its Inorganic Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Diarsenic Trioxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/14857/7/9/1. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2013. Development Support Document for Arsenic and Inorganic Arsenic Compounds. **Arsenic trioxide was not listed under PubChem.*

E.3.5 BOEHMITE [$AL_2O_3 \cdot H_2O$; CAS#1318-23-6]

**Also known as Aluminium Oxide Hydroxide*

ACUTE TOXICITY / IRRITATION

There was no acute toxicity information identified for boehmite.

Based on the ATSDR toxicological review, acute exposures to aluminium compounds may cause respiratory effects typically associated with inhalation of particulates and lung overload including pulmonary toxicity, thickening of the alveolar walls and increases in absolute lung weights, as demonstrated in animal studies (ATSDR, 2008).

TCEQ identified an acute exposure limit for aluminium oxide based on meeting the National Ambient Air Quality Standards (NAAQS) for PM. This is because for species of limited concern, the determination of the individual species impacts are not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

CHRONIC TOXICITY

There was no chronic toxicity information identified for boehmite.

Based on the ATSDR toxicological review, chronic inhalation exposures to aluminium may cause respiratory effects, including increases in alveolar macrophages, granulomatous lesions in the lungs and peribronchial lymph nodes, and increases in lung weight. The lung effects observed in humans and animals are suggestive of dust overload. Subtle neurological effects have also been observed in workers chronically exposed to aluminium dust or fumes. These effects include impaired performance on neurobehavioral tests (ATSDR, 2008).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	3.59 mg/m^3 (workers)	Pulmonary toxic effects	Chronic - animal (Gross *et al.*, 1973)	$UF_H = 3$ $UF_L = 3$ $UF_D = 3$	ECHA (2021)
ACGIH	**1 mg/m^3**	**Respiratory and neurological effects**	**Chronic - human (Sjogren & Elinder, 1992)**		**ACGIH (2008)** ***Surrogated to Al and its insoluble compounds***

	TCEQ	Must meet NAAQS	Increases in enzyme activities of alkaline phosphatase in the lavage fluid	Acute- animal (Thomson *et al.*, 1986)	-	TCEQ (2021) *Surrogated to PM*

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

European Chemical Agency (ECHA)

ECHA REACH listed a chronic inhalation limit for workers of 3.59 mg/m^3 for boehmite. The limit was based on Gross *et al.* (1973), an animal study that exposed 30 rats to aluminium oxide dust (2.49, 2.22 and 4.85 µm in size) within chambers for 6 months at a dose of 50 and 100 mg/m^3 and 12 months at a dose of 15 and 30 mg/m^3 for 6 hours per day, 5 days per week. A follow-up examination occurred 30 months after exposure. Effects observed included lipid pneumonitis, granulomatous inflammation and collagenous scars. Aluminium oxide was determined to act as a low cytotoxic, poorly soluble particulates (PSPs) causing pulmonary toxic effects, where the effects after inhalation are attributable to the particle per se rather than a substance specific toxicity. The LOAEL of 50 mg/m^3 from this study was selected as the point of departure based on respiratory and neurological effects. The LOAEL was adjusted for an 8-hr exposure day and differences in inhalation volume between rats and humans. An uncertainty factor of 3 was applied for intraspecies differences, 3 for the use of a LOAEL and 3 for database inadequacy (ECHA, 2021).

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH established a TLV-TWA-TWA of 1 mg/m^3 for aluminium and its insoluble compounds (including aluminium oxide and aluminium in bauxite ore dust). . The authors reviewed available literature and concluded that a urinary aluminium level of 100 µg/L (corresponding to an airborne concentration of 1.6 mg/m^3) was a critical concentration for development of neurological effects based on an occupational study by Sjogren and Elinder (1992). The study identified that long-term exposures to aluminium and aluminium compounds leading to body burdens equivalent to breathing 1.6 mg/m^3 for 40 years can result in an increased prevalence of neurological effects (ACGIH, 2008).

Texas Commission on Environmental Quality (TCEQ)

TCEQ identified a chronic exposure limit for aluminium oxide based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

GENOTOXICITY / MUTAGENICITY	A review conducted by ECHA based on aluminium compounds concluded the weight of evidence does not support a systemic mutagenic hazard for boehmite (ECHA, 2021).

REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for boehmite.
CARCINOGENICITY	Boehmite is not classifiable as a human carcinogen (ACGIH, 2008). Based on a review by ECHA, the weight of evidence does not support a systemic or local carcinogenic effect from exposure to aluminium hydroxide. Moreover, the current weight of evidence does not support an association between inhalation exposure to aluminium metal/aluminium oxide and cancers in the respiratory organs. The weight of evidence also does not support a systemic carcinogenic effect from exposure to aluminium metal and aluminium oxide (ECHA, 2021).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for boehmite.
SELECTED EXPOSURE LIMIT	The ACGIH limit for aluminium and its insoluble compounds is selected as it is based on chronic exposure in humans. The ECHA limit is based on an older animal study, and the TCEQ limit is based on exposures to particulate matter, rather than the toxicity of the COPC. Boehmite is an insoluble aluminium compound; therefore, the ACGIH limit is an appropriate surrogate. An additional uncertainty factor of 100 was applied to the ACGIH limit to account for sensitive individuals including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of **0.01 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2008. Toxicological profile for Aluminium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2008. Aluminium Metal and Insoluble Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Boehmite. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15111/11. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Boehmite was not listed under ATSDR.*

E.3.6 CALCIUM CANCRINITE [$(Na_2O \cdot Al_2O_3 \cdot 2SiO_2)_3 \cdot (CaCO_3)_2$]; CAS#12172-98-4]

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for calcium cancrinite.
CHRONIC TOXICITY	There was no chronic toxicity information identified for calcium cancrinite.
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for calcium cancrinite.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for calcium cancrinite.
CARCINOGENICITY	There was no carcinogenicity information identified for calcium cancrinite.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for calcium cancrinite.
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL **0.005 mg/m^3** used as the general ESL for metals with low toxicity for calcium cancrinite.
REFERENCES	Calcium cancrinite was not listed under ATSDR, ACGIH, ECHA, TCEQ or PubChem.

E.3.7 CERIUM OXIDE [CeO; CAS# 1306-38-3]

ACUTE TOXICITY / IRRITATION	As part of ECHA REACH for cerium oxide, an acute inhalation toxicity study was completed. One group of 10- to 12-week-old rats (5/sex) was exposed by nose-only inhalation of cerium oxide for 4 hours at an average concentration of 5.05 mg/L, and then observed for 15 days for clinical effects. No mortality occurred during the study. Labored breathing and ruffled fur were noted in 2 males just after exposure, which persisted in one male for 24 hours after exposure. There were no significant changes in body weight. At necropsy, the lungs of all animals were incompletely collapsed with diffuse whitish foci. As the inhalation LC50 was higher than 5.05 mg/L, cerium oxide was not considered acutely toxic according to UN/EU GHS criteria (ECHA, 2021). TCEQ adopted a short-term ESL for a one-hour averaging period of 50 µg/m^3 of cerium oxide based on the general ESL for metals with low toxicity (TCEQ, 2021).
CHRONIC TOXICITY	As part of the ECHA REACH for cerium oxide, a subchronic inhalation toxicity study was completed. Cerium oxide was exposed to 7-week-old rats (15/ sex) for 6 hours a day, 5 days a week, for 13 weeks, at concentrations of 0, 5, 50.5 or 507.5 mg/m^3, respectively) through nose-only inhalation. An overall NOAEL was not established in the study based on changes in hematology (females only), macroscopic observations at necropsy and histopathology at the

lowest concentration tested. However, the LOAEL was set at 5 mg/m^3 based on the increased incidence of lymphoid hyperplasia in the bronchial lymph nodes of rats of both genders. After considering the interspecies differences between rats and non-rodent mammals regarding location of the inhaled particles during chronic exposure, it was concluded that there were no significant effects to human health based on the study results. Also, no systemic toxic effects specific to cerium dioxide were observed. The observed effects were attributed to a "lung overload" inflammatory response in the rat following inhalation of poorly soluble particles of low toxicity and resulting "portal-of-entry" effects. It was concluded that the effects noted at the tested high concentrations were not relevant to occupational exposure (ECHA, 2021).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	--	-	-	-
ACGIH	-	-	-	-	-
TCEQ	**0.005 mg/m^3**	-	-	-	**TCEQ (2021)** ***Surrogated to general ESL for metals with low toxicity***

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

Texas Commission on Environmental Quality (TCEQ)

TCEQ adopted a long-term ESL of 5 µg/m^3 of cerium oxide based on the general ESL for metals with low toxicity (TCEQ, 2021).

GENOTOXICITY / MUTAGENICITY	No indication of genetic toxicity based on *in vitro* test results (Ames test and gene mutation assay in mammalian cells). (ECHA, 2021)
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	As part of the ECHA REACH for cerium oxide, several screening studies evaluating reproductive and developmental toxicity were completed. No significant effects were observed in the reproductive performance or systemic toxicity of parents or in the development of offspring from cerium oxide exposures (ECHA, 2021).
CARCINOGENICITY	There was no carcinogenicity information identified for cerium oxide.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for cerium oxide.
SELECTED EXPOSURE LIMIT	The TCEQ value of **0.005 mg/m^3** is selected as inhalation exposure limit for cerium oxide.

REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Cerium Dioxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15783/7/9/1. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 73963, Cerium dioxide", accessed online: https://pubchem.ncbi.nlm.nih.gov/compound/Cerium-dioxide. Last updated at October 2021. Last accessed at November 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Cerium oxide was not listed under ATSDR or ACGIH.*

E.3.8 CHROMIUM TRIOXIDE [Cr_2O_3; CAS#1308-38-9]

ACUTE TOXICITY / IRRITATION	Based on ATSDR's toxicological review, acute exposure to hexavalent chromium can develop asthma and other signs of respiratory distress, such as dyspnea, cough, and wheezing. Gastrointestinal effects have been associated with occupational acute exposure of humans to chromium compounds. Acute systemic and dermal allergic reactions have been observed in chromium sensitive individuals exposed to chromium via inhalation (ATSDR, 2012). TCEQ developed an acute (24 hr) AMCV of 1.3 µg/m^3 for hexavalent chromium particulate compounds, including chromium trioxide (TCEQ, 2021). The AMCV was derived from Glaser *et al.* (1990), an animal study where 8-week-old male Wistar rats (30 animals/group) were exposed for 22 h/d, 7 d/week to sodium dichromate at 0, 50, 100, 200, and 400 µg CrVI/m^3. Groups of 10 animals were sacrificed after 30 or 90 d of exposure or after 90 d of exposure with a 30-d recovery period. The $BMCL_{10}$ of 16 µg CrVI/m^3 based on an increase in relative lung weight was selected as the point of departure (POD). The POD was adjusted to a human equivalent concentration. An uncertainty factor (UF) of 3 was applied for extrapolation from animals to humans and an intraspecies UF of 10 to account for variability within the human population. A database UF of 1 was applied because while the acute database is limited, database quality is medium to high for intermediate duration exposure (e.g., studies in more than one species; two rat strains, rabbits) and a much longer duration exposure study (30-d subacute exposure, 22 h/d) was used to determine a 24-h acute ReV. An acute ESL (24 hr of 0.39 µg/m^3 was derived from the AMCV based on a target hazard quotient of 0.3 (TCEQ, 2014). Although acute AMCV/ESL values from TCEQ are usually derived based on a 1-hour exposure duration, studies evaluating adverse effects due to such short-term exposure to CrVI are very limited. The shortest duration studies available in the scientific peer-reviewed literature from which to identify an appropriate POD for derivation of short-term, health-protective air concentrations for CrVI involve intermediate (e.g., subacute) exposure duration. The resulting values are considered sufficiently health-protective of not only 24-h exposure, but also the intermittent exposure which may occur over intermediate exposure duration downwind of a permitted facility or source. (TCEQ, 2014)

CHRONIC TOXICITY

Based on ATSDR's toxicological review, chronic exposure to chromium can cause irritation to the lining of the nose, nose ulcers, runny nose, and breathing problems, such as asthma, cough, shortness of breath, or wheezing. The concentrations of chromium in air that can cause these effects may be different for different types of chromium compounds, with effects occurring at much lower concentrations for chromium (VI) compared to chromium (III). Long-term exposure can also cause lung cancer based on occupational studies (ATSDR, 2012).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	0.0002 mg/m^3	Respiratory irritation and lung cancer	Chronic – human (Lindberg & Hedenstierna, 1983; Glaser *et al*, 1985 &1990)	-	ACGIH (2018)
TCEQ	**0.0000043 mg/m^3**	**Lung cancer**	**Chronic - human (Derelanko *et al*., 1999)**	-	**TCEQ (2014)**

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH derived a TLV-TWA of 0.0002 mg/m^3 for hexavalent chromium compounds, including chromium trioxide. The TLV-TWA was based on Lindberg and Hedenstierna (1983), who studied the effects of various exposure concentrations (0.002-0.02 mg/m^3) of Cr(VI) in chrome platers and observed a NOAEL range of 0.0002-0.0012 mg/m^3 protective of severe irritation of the upper and lower respiratory tract, and from decreases in lung function. Additionally, the most reliable animal data on long-term inhalation exposures to Cr(VI) came from 30-and 90-day exposures to aerosols of sodium dichromate in rats (Glaser *et al*., 1985, 1990), in which a human-equivalent LOAEL of

	0.0022 mg/m^3 was derived, which was further adjusted to obtain a NOAEL of 0.0002 mg/m^3 (ACGIH, 2018). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ developed a long-term AMCV of 0.0043 µg/m^3 for hexavalent chromium particulate compounds, including chromium trioxide (TCEQ, 2021). The AMCV was derived from Crump at al. (2003) and Gibb *et al*. (2000), epidemiological studies that looked at the association between CrVI exposure and lung cancer in chromate production worker cohorts in Ohio and Maryland, USA. These cohorts are relatively large, have extensive follow-up, and documentation of historical CrVI exposure levels. The Crump (2003) study included 482 workers employed for at least one-year from1940 to 1972 and followed through 1997 (14,443 person-years). Cumulative exposure to CrVI was significantly associated with increased lung cancer risk. The Gibb (2000) study evaluated lung cancer mortality in a cohort of 2,357 male chromate production workers in Baltimore, Maryland hired during 1950 to1974, with mortality followed through 1992. The long-term AMCV was calculated based on an inhalation unit risk factor (URF) of 2.3 × 10-3 per µg/m^3 derived from these studies and a no significant risk level of 1 in 100,000 excess cancer risk (TCEQ, 2014).
GENOTOXICITY / MUTAGENICITY	Based ATSDR's toxicological review, chromium (VI) is genotoxic, and its genotoxicity has been related to the solubility, and therefore, to the bioavailability to the target organs. *In vitro* studies indicated that soluble chromium (VI) compounds are mutagenic (ATSDR, 2012).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Based ATSDR's toxicological review, sperm damage and damage to the male reproductive system has been seen in laboratory animals exposed to chromium (VI) (ATSDR, 2012).
CARCINOGENICITY	The IARC and the US EPA have determined that chromium (VI) compounds are known human carcinogens following inhalation. In workers, inhalation of chromium (VI) has been shown to cause lung cancer. Chromium (VI) also causes lung cancer in animals (ATSDR, 2012).
SENSITIVE SUBPOPULATIONS	Based ATSDR's toxicological review, it is likely that health effects seen in children exposed to high amounts of chromium will be similar to the effects seen in adults. It is unknown if exposure to chromium will result in birth defects or other developmental effects in humans. Some developmental effects have been observed in animals exposed to chromium (VI) (ATSDR, 2012).
SELECTED EXPOSURE LIMIT	The TCEQ 24 hr limit of **0.0013 mg/m^3** is selected for chromium trioxide to protect against developmental effects. As discussed by TCEQ, this limit is considered sufficiently health-protective of not only acute exposure over 24-hrs, but also the intermittent exposure which may occur over intermediate exposure duration downwind of a permitted facility or source. (TCEQ, 2014) The TCEQ chronic limit of **0.0000043 mg/m^3** is selected for chromium trioxide to protect against the development of lung cancer. This exposure limit is based on an inhalation unit risk factor (URF) of 2.3 × 10-3 per µg/m^3 and a no significant risk level of 1 in 100,000 excess cancer risk. This exposure limit is based on a more recent primary study and is considered protective of the general population.

REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological Profile for Chromium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2018. Chromium and Inorganic Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Chromium (III) oxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15477/7/9/1. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 517277, Chromium (III) oxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Chromium_III_-oxide. Last updated in October 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS AMCV Summary Report. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2014. Development Support Document for Chromium – Hexavalent Chromium (Particulate Compounds)

E.3.9 COPPER OXIDE [CuO; CAS#1317-38-0]

ACUTE TOXICITY / IRRITATION	Based on ATSDR's toxicological review for copper, acute inhalation exposures can cause respiratory irritation of nose and throat. Other symptoms such as cough, sneeze, thoracic pain and runny nose were also observed (ATSDR, 2004). TCEQ adopted the short-term ESL for a one-hour averaging period of 10 µg/m^3 from the NIOSH/OSHA/ACGIH 8 hr TWA for copper of 1 mg/m^3 with a safety factor of 100 (TCEQ, 2021).
CHRONIC TOXICITY	Based on ATSDR's toxicological review, chronic inhalation exposure to copper can cause respiratory, hematological, and hepatic effects in human. Copper is considered the etiologic agent in the occupational disease referred to as "vineyard sprayer's lung". Decreased hemoglobin and erythrocyte levels have been observed in workers exposed to airborne copper levels of 0.64–1.05 mg/m^3. But results of hair analysis reveal that the workers were also exposed to iron, lead, and cadmium. Hepatomegaly was observed in workers involved in grinding and sieving copper dust, the exposure levels ranged from 111 to 434 mg Cu/m^3 (ATSDR, 2004). Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	**1 mg/m^3 (dust and mists)***	**Ocular, dermal, respiratory tract and mucous membrane irritation**	**Acute - human (Whitman, 1957; Gleason, 1968; Luxon S.G, 1972)**		**ACGIH (2001)**

	TCEQ	0.001 mg/m^3	Adopted from NIOSH/OSHA/ACGIH 8 hr TWA	-	Safety factor of 1000 applied by TCEQ	TCEQ (2021)
	Notes: **Bold = selected limit** UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 1 mg/m^3 for copper dusts and 0.2 mg/m^3 for mists. Several studies were used to support this value. Whitman (1957) found that exposure to concentrations of copper fume between 0.02 to 0.4 mg/m^3 for short periods from welding operations did not cause any complaints. Gleason (1968) identified a condition similar to metal fume fever in workers exposed to metallic copper dust at concentrations of 0.1 mg/m^3. Finally, data from industry, specifically for copper-welding operations and copper-metal refining in Great Britain (Luxon S.G, 1972) supports the view that no adverse effects develop from exposure to fumes up to 0.4 mg/m^3 of copper. No further discussion on the derivation of the TLV-TWA was available. The TLV-TWA values are intended to protect against ocular, dermal, respiratory tract, and mucous membrane irritation (ACGIH, 2011). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ adopted the long-term ESL/AMCV of 1 µg/m^3 for copper oxide from the NIOSH/OSHA/ACGIH 8 hr TWA for copper of 1 mg/m^3 with an additional safety factor of 1000 (TCEQ, 2021).					
GENOTOXICITY / MUTAGENICITY	Copper and copper compounds are not considered genotoxic (ECHA, 2021).					
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Based on ATSDR's toxicological review, it is unknown if copper causes birth defects or other developmental effects in humans. Studies in animals suggest that high levels of copper may cause a decrease in fetal growth (ATSDR, 2004). ECHA (2021) concluded that copper has no reproductive or developmental toxicity potential.					
CARCINOGENICITY	It is uncertain if copper can cause cancer in humans. The US EPA has determined that copper is not classifiable as to human carcinogenicity (ATSDR, 2004).					
SENSITIVE SUBPOPULATIONS	Animal studies suggest that young children may have more severe effects than adults from copper exposure, but it is uncertain if this would occur in humans. There is a very small percentage of infants and children who are unusually sensitive to copper (ATSDR, 2004).					
SELECTED EXPOSURE LIMIT	The ACGIH limit of 1 mg/m^3 is selected for copper oxide since the TCEQ limit is adopted from this limit. An additional uncertainty factor of 1000 was applied to account for acute to chronic uncertainty and to ensure protection of sensitive individuals including children, asthmatics and elderly and the general public from continuous exposures. The resulting adjusted exposure limit of 0.001 mg/m^3 is applied in the quantitative risk analysis.					

REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological Profile for Copper. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2011. Copper. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Copper Oxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15443/7/8 . Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Copper oxide was not listed under PubChem.*

E.3.10 GALLIUM TRIOXIDE [Ga_2O_3; CAS#12024-21-4]

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for gallium trioxide.
CHRONIC TOXICITY	There was no chronic toxicity information identified for gallium trioxide.
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for gallium trioxide.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for gallium trioxide.
CARCINOGENICITY	There was no carcinogenicity information identified for gallium trioxide.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for gallium trioxide.
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL 0.005 mg/m^3 used as the general ESL for metals with low toxicity for gallium trioxide.
REFERENCES	No information with respect to the toxicity of gallium trioxide or gallium was available from ACGIH, ECHA, TCEQ, PubChem or ATSDR.

E.3.11 GYPSUM [$CaSO_4 \cdot 2(H_2O)$; CAS#10101-41-4]

**Also known as Calcium Sulfate Dihydrate*

<table>
<tr><td>ACUTE TOXICITY / IRRITATION</td><td>Acute exposure to gypsum may cause irritation to eyes, skin, mucous membrane, cough, sneezing, and rhinorrhea (PubChem, 2021)

TCEQ identified an acute exposure limit for gypsum based on meeting the National Ambient Air Quality Standards (NAAQS) for PM. This is because for species of limited concern, the determination of the individual species impacts is not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).</td></tr>
<tr><td>CHRONIC TOXICITY</td><td>Based on the toxicological review by ACGIH, chronic inhalation exposures to calcium sulphate may cause pneumonia or other pulmonary effects. Slight lung pigmentation and lung collapse were also found. Moderate lymph node enlargement was frequently observed as well (ACGIH, 2006).

Inhalation exposure limits protective of chronic health are summarized below:
<table>
<tr><th>AGENCY</th><th>VALUE</th><th>HEALTH ENDPOINT</th><th>STUDY TYPE</th><th>UF</th><th>SOURCE</th></tr>
<tr><td>ECHA</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ACGIH</td><td>10 mg/m^3</td><td>Respiratory tract irritation</td><td>Acute – human (Cain et al., 2004)</td><td>*</td><td>ACGIH (2006)</td></tr>
<tr><td>TCEQ</td><td>Must meet NAAQS</td><td>-</td><td>-</td><td>-</td><td>TCEQ (2021) Surrogated to PM</td></tr>
</table>
Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH derived a TLV-TWA of 10 mg/m^3 for calcium sulphate (including the dihydrate). The TLV-TWA was derived from Cain et al. (2004). who exposed 12 individuals to varying concentrations of calcium sulphate (10, 20, and 40 mg/m^3) during exercise for a total of 20 minutes. It was reported that chemesthetic effects on the nose and throat were present only at the 40 mg/m^3 level; no effects to the eye, nasal secretion, nasal resistance, or mucociliary transport were observed at the other exposure levels. Although limited data exists, a TLV-TWA of 10 mg/m^3 is recommended based on lowest exposure dose in the Cain (2004) study to protect against long-term respiratory health effects as demonstrated in both animal and human studies following exposure to calcium sulphate (ACGIH, 2006).</td></tr>
</table>

	Texas Commission on Environmental Quality (TCEQ) TCEQ identified a chronic exposure limit for gypsum based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for gypsum.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for gypsum.
CARCINOGENICITY	There was no carcinogenicity information identified for gypsum.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for gypsum.
SELECTED EXPOSURE LIMIT	The ACGIH limit of 10 mg/m^3 is selected for gypsum. An additional uncertainty factor of 1000 was applied to account for acute to chronic exposure uncertainty and sensitive individuals including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of **0.01 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2006. Calcium Sulfate. National Center for Biotechnology Information. "PubChem Compound Summary for CID 24928, Calcium sulfate dihydrate" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Calcium-sulfate-dihydrate. Last updated in October 2021. Last accessed October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Gypsum was not listed under ATSDR or ECHA.*

E.3.12 HEMATITE [Fe_2O_3; CAS#1317-60-8]

**Also known as Iron Oxide*

ACUTE TOXICITY / IRRITATION	Based on the ACGIH toxicological review, acute exposures to iron oxide may cause alveolar macrophages and changes to lung morphology (ACGIH, 2006). It was concluded by ECHA that hematite is irritating to the skin and corrosion to the eyes. ECHA REACH provide acute exposure limits for hematite of 0.18 mg/m^3 for workers and 0.09 mg/m^3 for the general public; however, there was no further details on the primary study or how these limits were derived (ECHA, 2021). TCEQ identified an acute exposure limit for hematite based on meeting the National Ambient Air Quality Standards (NAAQS) for PM. This is because for species of limited concern, the determination of the individual species impacts is not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

CHRONIC TOXICITY

Based on ACGIH's toxicological review, chronic exposures to iron oxide may contribute to the carcinogenicity of other compounds (e.g., PAHs) in mixed exposure environments. Occupational studies have shown that long-term exposure may cause non-specific inflammatory responses and development of X-ray changes in the lung. Pulmonary siderosis has been identified in chest X-rays associated with deposition and collection of iron oxide in the lungs from relatively high level (10-700 mg/m^3) exposures for prolonged periods; however, this has not been associated with clinical changes. Experimental studies have shown that the instillation or inhalation of iron oxide can cause a mild nonspecific inflammatory response to the presence of particles in the lungs (ACGIH, 2006).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	**5 mg/m^3**	**Non-specific inflammatory responses; Pulmonary siderosis**	**Chronic – humans (Keenan K *et al.*, 1989; Lay JC *et al.*, 1999; Grant MM *et al.*, 1979)**		**ACGIH (2006)**
TCEQ	Must meet NAAQS	-	-	-	TCEQ (2021) *Surrogated to PM*

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

An ACGIH review derived a TLV-TWA of 5 mg/m^3 (respirable particulate mass) for iron oxide (hematite). The TLV-TWA is based on several experimental human and animal studies (Keenan K *et al,* 1989; Lay JC *et al*, 1999) which have demonstrated that instillation of iron oxide into the lungs caused a mild inflammatory response but showed no evidence of fibrogenic potential. Pulmonary siderosis has been identified in chest X-rays associated with deposition and collection of iron oxide in the lungs from relatively high level (10-700 mg/m^3) exposures for prolonged periods based on occupational exposures (Jones *et al*., 1972 and Teculescu *et al.,* 1973). Additionally, an inhalation study in rabbits (Grant MM et al, 1979) demonstrated that iron oxide increased the number of lavagable pulmonary macrophages at about 200 mg/m^3 and increased phagocytic activity at 20 mg/m^3 for 2 hrs. Limited discussion is available as to how the specific TLV-TWA was derived from these studies. The TLV-TWA-TWA of 5 mg/m^3 is recommended for occupational exposure to iron oxide to minimize the potential for nonspecific inflammatory responses and development of x-ray changes in the lung (ACGIH, 2006).

	Texas Commission on Environmental Quality (TCEQ) TCEQ identified a chronic exposure limit for hematite based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for hematite.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There is no reason to suggest that any effect on reproduction is likely (ECHA, 2021).
CARCINOGENICITY	Hematite was not classifiable as a human carcinogen based on negative inhalation and intratracheal studies with rodents (ACGIH, 2006).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for hematite.
SELECTED EXPOSURE LIMIT	The ACGIH limit of 5 mg/m^3 is selected for hematite since it is based on chronic toxicological effects reported in humans from iron oxide exposure. The TCEQ limit is surrogated to PM and not based on the specific toxicity of the COPC. An additional uncertainty factor of 100 was applied to account for sensitive individuals including children, asthmatics and elderly to ensure protection of the general public from continuous exposures. The resulting adjusted exposure limit of **0.05 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2006. Iron Oxide. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Calcium Carbonate. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/7586/7/1. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Hematite was not listed under ATSDR or PubChem.*

E.3.13 HYDROGARNET [$3(CaO)\cdot Al_2O_3\cdot SiO_2\ 4(H_2O)$; CAS#68131-78-8]

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for hydrogarnet.
CHRONIC TOXICITY	There was no chronic toxicity information identified for hydrogarnet.
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for hydrogarnet.

REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for hydrogarnet.
CARCINOGENICITY	There was no carcinogenicity information identified for hydrogarnet.
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL 0.005 mg/m^3 used as the general ESL for metals with low toxicity for hydrogarnet.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for hydrogarnet.
REFERENCES	Hydrogarnet was not listed under ATSDR, ACGIH, ECHA, TCEQ or PubChem.

E.3.14 LEAD OXIDE [PbO; CAS#1317-36-8]

ACUTE TOXICITY / IRRITATION

Based on ATSDR's toxicological review, no controlled studies in humans have evaluated the acute toxicity of lead or lead poisoning. The available information is anecdotal from case reports. Acute lead toxicity is characterized by symptoms of abdominal pain/colic, vomiting, constipation, peripheral neuropathy, and cerebral edema and encephalopathy, which can lead to seizures, coma, and death. However, the data have not been sufficient to establish a dose-response relationship for acute toxicity from lead (ATSDR, 2020).

Sparingly soluble lead compounds do not exhibit irritant or corrosive properties in acute inhalation studies. There are no reports of respiratory irritation in occupationally exposed workers (ECHA, 2021).

No acute exposure limits protective of inhalation of lead were identified.

CHRONIC TOXICITY

Based on ATSDR's toxicological review, the effects of lead are the same whether it enters the body by inhalation or ingestion. Lead can affect almost every organ and system in your body. The nervous system is the main target for lead toxicity in children and adults. Long-term exposure can result in decreased learning, memory, and attention, and weakness in fingers, wrists, or ankles. Lead exposure can cause anemia (low iron in the blood) and damage to the kidneys. It can also cause increases in blood pressure, particularly in middle-aged and older individuals. Exposure to high lead levels can severely damage the brain and kidneys and can cause death. In pregnant women, exposure to high levels of lead may cause a miscarriage. In men, it can cause damage to reproductive organs (ATSDR, 2020).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)

	ACGIH	0.05 mg/m^3	Blood dyscrasias, reduced nerve conduction velocities, kidney dysfunction, spermatogenesis, impaired intellectual development in children exposed to lead during gestation, and carcinogenicity	Chronic - human (including Moore *et al*, 1989, McMichael A.J, 1988, and Coonin G.H, 1989)	-	ACGIH (2001)
	TCEQ	**0.00015 mg/m^3** ***(not to be exceeded over a 3-month rolling average)***	**IQ loss in children**	**Chronic – human (USEPA, 2008)** ****This criteria was reviewed in 2016 with no revisions***	-	**TCEQ (2021)** ***Adopted from the NAAQS***
	Notes: **Bold = selected limit** UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH's review derived a TLV-TWA of 0.05 mg/m^3 for lead and inorganic compounds based on experimental and epidemiological literature (including Moore *et al*, 1989, McMichael A.J, 1988, and Coonin G.H, 1989). Based on these studies, it was concluded that workplace conditions that keep a woman's blood lead level below 30 µg/dL will protect her ability to bear children that can develop normally. A TLV-TWA of 0.05 mg/m^3 would contribute to an airborne, work-related fraction of blood lead concentration of 9.5 µg//dL; which considered additional contributions from community sources and from non-airborne workplace contamination whereby total blood lead concentrations should be kept below the 30 µg/dL. A TLV-TWA of 0.05 mg/m^3 is intended to protect against blood dycrasias, reduced nerve conduction velocities, kidney dysfunction, spermatogenesis, impaired intellectual development in children exposed to lead during gestation, and carcinogenicity (ACGIH, 2001). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ adopted a long-term ESL/AMCV for lead oxide from the NAAQS value for lead of 0.00015 mg/m^3, which is not to be exceeded over a 3-month rolling average (TCEQ, 2021). The limit was derived by the NAAQS using estimated mean IQ loss for children in the USA related to lead concentrations in air. Under the air-to-blood ratio of 1:7, the air-related IQ loss is below 2-points at lead concentrations of 0.00015 mg/m^3 (US EPA, 2008). The US EPA reviewed these criteria in 2016 and decided to retain the value with no revisions (TCEQ, 2021).					
GENOTOXICITY / MUTAGENICITY	Based on ATSDR's toxicological review, lead has been shown to be genotoxic through epidemiological studies, in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. Studies in occupationally exposed populations have found significant correlations between DNA breaks, decreased glutathione levels in the lymphocytes, and increased					

	production of ROS, which may indicate oxidative stress as a possible mechanism for this response (ATSDR, 2020).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Children can be exposed to lead in their environment and before birth from lead in their mother's body. At lower levels of exposure, lead can decrease mental development, especially learning, intelligence, and behavior. Physical growth may also be decreased. Some effects of lead poisoning in a child may continue into adulthood (ATSDR, 2020).
CARCINOGENICITY	The US EPA has classified lead as a probable human carcinogen. The IARC has determined that inorganic lead is probably carcinogenic to humans (ATSDR, 2020).
SENSITIVE SUBPOPULATIONS	Children are more vulnerable to lead poisoning than adults because their nervous system is still developing. Exposure to lead during pregnancy can also result in premature births (ATSDR, 2020).
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.00015 mg/m^3** is selected for lead oxide since it is protective of at-risk groups including child-bearing females and developing fetus and was reviewed in 2016. The ACGIH exposure limit is outdated (2001), less stringent and is based only on occupational worker exposures.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2020. Toxicological Profile for Lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Hygienists (ACGIH). 2001. Lead and Inorganic Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Lead Monoxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15541/7/9/3. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 14827, Lead monoxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Lead-monoxide. Last updated in October 2021. Last accessed October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. US EPA. 2008. National Ambient Air Quality Standard for Lead; Final Rule. Accessed online at: https://www.govinfo.gov/content/pkg/FR-2008-11-12/pdf/E8-25654.pdf. Last accessed: October 2021.

E.3.15 MANGANESE OXIDE [MnO; CAS#1344-43-0]

ACUTE TOXICITY / IRRITATION

Based on ATSDR's toxicological review of workers exposure, the inhalation of large quantities of dust or fumes containing manganese may cause lung irritation, which could lead to pneumonia. Similar respiratory effects have been observed in animals (ATSDR, 2012).

TCEQ developed an acute (1 hr) AMCV of 5.0 µg/m^3 for manganese oxide based on studies with manganese and inorganic manganese compounds (TCEQ, 2021). The AMCV was derived from Dorman *et al*. (2005), an animal study with Rhesus monkeys exposed through inhalation for 6 h/d, 5 d/wk, for 3 weeks. The LOAEL of 1.5 mg/m^3 based on inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation) was selected as the point of departure (POD). The POD was adjusted for a 1 hr exposure concentration and a human equivalent concentration. An uncertainty factor (UF) of 2 was used for extrapolation from a LOAEL to a NOAEL; a UF of 10 was used for intra human variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions); an UF of 3 was used to account for potential toxicodynamic differences between rhesus monkeys and humans; and an UF of 6 was used for limitations/uncertainties in the acute/subacute database including lack of toxicological data on humans exposed to soluble Mn and on developmental effects. An acute (1 hr) ESL of 2.7 µg/m^3 was calculated from the AMCV based on a target HQ of 0.3 (TCEQ, 2017).

CHRONIC TOXICITY

Based on ATSDR's toxicological review of occupational studies, chronic inhalation of manganese most commonly causes behavioral changes and other nervous system effects, which include movements that may become slow and clumsy. The manganese concentrations that cause effects such as slowed hand movements in some workers are approximately twenty thousand times higher than the concentrations normally found in the environment. Magnesium has been found in some workers exposed to manganese concentrations about a million times higher than normal air concentrations of manganese (ATSDR, 2012).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	-
ACGIH	0.02 mg/m^3 (respirable particulate matter) 0.1 mg/m^3 (inhalable particulate matter)	Central nervous system impairment	Chronic – human (Roles *et al*., 1992)	-	ACGIH (2003)
TCEQ	**0.00084 mg/m^3**	**Abnormal eye-hand coordination scores in humans**	**Chronic – human (Roels *et al*., 1992)**	**$UF_H = 10$ $UF_D = 6$**	**TCEQ (2017)**
Notes:					

	Bold = selected limit UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 0.02 mg/m^3 (respirable particulate matter) and 0.1 mg/m^3 (inhalable particulate matter) for manganese, elemental and inorganic compounds (including manganese oxide). The TLV-TWA was based on Roels *et al*. (1992), a cross-sectional study that found neurotoxic effects in Belgian workers and suggested that an 8-hr TWA of 0.036 mg/m^3 (respirable aerosol) would protect most workers from the CNS effects of manganese. Based on this data, the exposure levels for impaired hand steadiness affecting 5%, 2.5%, and 1% of individuals were derived. A level of 0.02 mg/m^3 (respirable aerosol) would lead to impaired hand steadiness (detected with subtle tests but not clinically) in 2.5% of workers, which was selected as the TLV-TWA for the respirable fraction. The TLV-TWA of 0.02 mg/m^3 is 1.5-2 times lower than the range of LOAEL values observed in several studies and further analysis of the data by ATSDR using the benchmark dose approach produced a $BMDL_{10}$ of 0.07 mg/m^3 for the respirable fraction. A ratio of 5:1 for inhalable to respirable concentrations of manganese was applied to produce an estimated inhalable aerosol limit of 0.1 mg/m^3. The TLV-TWA-TWA values are intended to protect against central nervous system impairment (ACGIH, 2003). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ developed a long-term AMCV of 0.00084 mg/m^3 for manganese and inorganic manganese compounds, including manganese oxide (TCEQ, 2021). The ESL was derived from Roels *et al.* (1992), an occupational study with 92 male workers in a dry alkaline battery factory. Total and respirable Mn dust concentrations were measured using personal air sampling in different occupational areas within the factory. Workers were exposed for an average duration of 5.3 years (range 0.2-17.7 years) to average (geometric mean) concentrations of 0.215 and 0.948 mg Mn/m^3 in respirable and total dust, respectively. The $BMDL_{10}$ based on abnormal eye-hand coordination scores was selected as the point of departure (POD), adjusted for continuous exposure. An uncertainty factor (UF) of 10 was applied to account for intra-human variability and 6 for limitations and uncertainties in the database, including lack of epidemiological data for humans chronically exposed to soluble forms of Mn and lack of developmental studies. An ESL of 0.25 µg/m^3 was calculated from the AMCV based on a target hazard quotient of 0.3 (TCEQ, 2017).
GENOTOXICITY / MUTAGENICITY	The results of *in vitro* studies show that at least some chemical forms of manganese have mutagenic potential. However, as the results of *in vivo* studies in mammals are inconsistent, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds. *In vitro* assays in mammalian cells gave conflicting results concerning manganese mutagenicity. No studies were located regarding genotoxic effects in animals after inhalation exposure to inorganic manganese (ATSDR, 2012).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Human studies reveal conflicting evidence for whether occupational exposure to manganese causes adverse reproductive effects. Effects reported may occur as a secondary result of neurotoxicity, but there is no information on any direct effect manganese may have on the

	reproductive organs. No information was found regarding reproductive effects in women. (ATSDR, 2012)
CARCINOGENICITY	Manganese oxide is not classifiable as a human carcinogen (PubChem, 2021).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for manganese oxide.
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.00084 mg/m^3** is selected for manganese oxide. Both the ACGIH and TCEQ limits are based on the same primary study, but the TCEQ limit is protective of the general population including sensitive individual and was derived more recently.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2003. Manganese, Elemental and Inorganic Compounds. Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological Profile for Manganese. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service National Center for Biotechnology Information. "PubChem Compound Summary for CID 14940, Manganese(II) oxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Manganese_II_-oxide. Accessed 13 October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2017. Development Support Document for Manganese and Inorganic Manganese Compounds. **Manganese oxide was not listed under ECHA.*

E.3.16 NIOBIUM PENTOXIDE [Nb_2O_5; CAS#1313-96-8]

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for niobium pentoxide. Niobium pentoxide is not irritating to the skin or eyes (ECHA, 2021). No acute exposure limits protective of inhalation of niobium pentoxide were identified.
CHRONIC TOXICITY	As part of the ECHA REACH for niobium pentoxide, a repeated oral dose study was completed. Niobium pentoxide (Nb_2O_5) was administered in deionised water to the male (28-29 days) and female (maximum 54 days) Wistar rats at dosages of 250, 500 and 1000 mg/kg. There were no major toxicological findings. Given that the NOAEL is greater than 1000 mg/kg body weight in males and females, toxicological testing from other routes of exposure was not necessary (ECHA, 2021). No chronic exposure limits protective of inhalation of niobium pentoxide were identified.

GENOTOXICITY / MUTAGENICITY	Niobium pentoxide was negative, with and without metabolic activation, in a full battery of *in-vitro* genotoxicity tests (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There is no evidence of reproductive or developmental toxicity from niobium pentoxide (ECHA, 2001).
CARCINOGENICITY	There was no carcinogenicity information identified for niobium pentoxide/
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL **0.005 mg/m^3** used as the general ESL for metals with low toxicity for niobium pentoxide.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for niobium pentoxide.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Diniobium Pentoxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14981/7/9/2. Last updated in July 2021. Last accessed in October 2021. **Niobium pentoxide was not listed under ATSDR, ACGIH, PubChem, or TCEQ.*

E.3.17 PEROVSKITE [$CaTiO_3$; CAS#12049-50-2]

**Also known as Calcium Titanium Trioxide*

ACUTE TOXICITY / IRRITATION	ECHA concluded that it was not required to investigate the acute toxicity of perovskite via the inhalation and dermal routes in accordance with Annex VII of REACH (ECHA, 2021).
CHRONIC TOXICITY	There was no chronic toxicity information identified for perovskite.
GENOTOXICITY / MUTAGENICITY	Calcium titanium trioxide was determined to be non-mutagenic with and without metabolic activation (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for perovskite.
CARCINOGENICITY	There was no carcinogenicity information identified for perovskite.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for perovskite.
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL **0.005 mg/m^3** used as the general ESL for metals with low toxicity for perovskite.

REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Perovskite. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/23366/7/7/1. Last accessed in October 2021. **Perovskite was not listed under ATSDR, ACGIH, PubChem, or TCEQ.*

E.3.18 SODIUM FLUORIDE [NaF; CAS#7681-49-4]

ACUTE TOXICITY / IRRITATION

Fluorine and hydrogen fluoride are very irritating to the skin, eyes, and respiratory tract. At high levels, such as may occur through exposure from an industrial accident, hydrogen fluoride may also damage the heart (ATSDR, 2003).

TCEQ developed an acute (1 hr) AMCV of 57 µg/m^3 for sodium fluoride based on soluble inorganic fluorides (TCEQ, 2021). The ESL was derived from Lund *et al.* (1999), which was a study with 19-23 healthy non-smoking male volunteers. The volunteers were exposed through inhalation of 0.2-0.6 (low exposure), 0.7-2.4 (intermediate exposure), or 2.5-5.2 mg/m^3 (high exposure) of hydrogen fluoride for one hour. The NOAEL of 0.6 mg/m^3 based on upper respiratory tract and eye irritation and respiratory tract inflammation was selected as the point of departure (POD). An uncertainty factor (UF) of 10 was applied to account for human variability. An UF of 1 for database uncertainty was applied because the overall quality of the studies was high with adequate supportive human and animal studies. An acute (1 hr) ESL of 17 µg F/m^3 was calculated from the AMCV based on a target hazard quotient of 0.3 (TCEQ, 2015).

CHRONIC TOXICITY

Based on ATSDRs toxicological review, chronic exposure to high levels of fluorine, hydrogen fluoride, and fluorides may cause denser bones. However, if exposure is high enough, these bones may be more fragile and brittle and there may be a greater risk of breaking the bone. (ATSDR, 2003).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	2.5 mg/m^3	Irritation of eyes and respiratory tract; disabling bone	Chronic - human (Derryberry *et al.*, 1963)	-	ACGIH (2001)
TCEQ	**0.027 mg/m^{3*}**	**Increased bone density and skeletal fluorosis**	**Chronic - human (Derryberry *et al.*, 1963)**	**$UF_H = 10$ $UF_D = 1$**	**TCEQ (2015)**

Notes:

Bold = selected limit

*Adjusted from the ESL of 0.0081 mg/m^3, which represents a target HQ of 0.3

	UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 2.5 mg/m^3 for inorganic fluorides. The TLV-TWA is based on Derryberry *et al*, (1963), which found no bone changes in a group of workers exposed at concentrations of fluoride averaging 2.65 mg/m^3, while such changes were detected in 17 workers with exposures averaging 3.38 mg/m^3. A TLV-TWA of 2.5 mg/m^3 is intended to protect against irritation of eyes and respiratory tract, as well as disabling bone changes due to fluorosis from long-term exposure (ACGIH, 2001). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ developed a long-term ESL of 0.0081 mg/m^3 for sodium fluoride based on soluble inorganic fluorides (TCEQ, 2021). The ESL was derived from Derryberry *et al*. (1963), which was an occupational study where fluoride exposure levels, urinary monitoring, and the health effects from fluoride were evaluated on 74 male workers in a fertilizer manufacturing plant. The length of employment for these workers ranged from 4.5 to 25.9 years (average 14.1 years) with 76% of workers having over 10 years of employment. The $BMCL_{10}$ for increased bone density and skeletal fluorosis was selected as the point of departure (POD). The POD was adjusted for continuous exposure and non-occupational ventilation rates. An uncertainty factor (UF) of 10 was applied to account for human variability. An UF of 1 was used for database uncertainty because human studies investigating a wide range of health endpoints were available and the overall quality of the key studies is high. It was not necessary to incorporate a UF to adjust for the use of a subchronic study since the average exposure duration of 14.1 years is more than 10% of the life span in humans. Therefore, the study was considered chronic. A final reference value of 0.027 mg/m^3 was derived and the final ESL was based on a target hazard quotient of 0.3 (TCEQ, 2015).
GENOTOXICITY / MUTAGENICITY	Both positive and negative results have been reported in *in vitro* genotoxicity studies and *in vivo* studies have indicated no genotoxicity. Fluoride salts are not expected to be genotoxic (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Studies on the developmental toxicity of fluoride are focused on oral administration in animals mainly through drinking water, with derived NOAELs for sodium fluoride ranging between 150 and 400 ppm for maternal and developmental toxicity (ECHA, 2021).
CARCINOGENICITY	Fluoride salts are not likely to present a risk of carcinogenicity based on the results of carcinogenicity studies in rodents (ECHA, 2021). ATSDR has found that most studies examining individuals living in areas with fluoridated water or naturally high levels of fluoride in drinking water did not find an association between fluoride and cancer risk. Two animal cancer studies were inconclusive. IARC has determined that the carcinogenicity of fluoride to humans is not classifiable. (ATSDR, 2003).
SENSITIVE SUBPOPULATIONS	No studies have addressed whether low levels of fluoride may cause birth defects in humans. Birth defects have not been found in most animal studies (ATSDR, 2003).

SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.027 mg/m^3** is selected for sodium fluoride. The ACGIH and TCEQ limits are based on the same primary study, but the TCEQ limit was derived more recently and is protective of exposures in the general population including sensitive individuals such as children, asthmatics and elderly.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological Profile for Fluorine, Hydrogen Fluoride, and Fluorides. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Fluorides. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Calcium Carbonate. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16050/7/8. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2015. Development Support Document for Hydrogen Fluoride and Other Soluble Inorganic Fluorides. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Sodium fluoride was not listed under PubChem.*

E.3.19 SODIUM OXALATE [$C_2O_4 \cdot 2Na$; CAS#62-76-0)

ACUTE TOXICITY / IRRITATION

There was no acute toxicity information identified for sodium oxalate.

TCEQ adopted the short-term ESL for a one hour averaging period of 10 µg/m^3 for sodium oxalate from the NIOSH/OSHA/ ACGIH 8 hr exposure limit for oxalic acid of 1 mg/m3 with a safety factor of 100 (TCEQ, 2021).

CHRONIC TOXICITY

There was no chronic toxicity information identified for sodium oxalate.

Inhalation exposure limits protective of chronic health are summarized below for oxalic acid:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	1 mg/m^3	Eye, skin, and upper respiratory tract irritation based on acidity.	Chronic - human (Leung & Paustenbach., 1990)	-	ACGIH (2015) *Surrogated to oxalic acid*
TCEQ	**0.001 mg/m^3**	**Based on NIOSH/OSHA/ ACGIH**	-	**TCEQ applied an additional safety factor 1000**	**TCEQ (2021)** ***Surrogated to oxalic acid***

	Notes: **Bold = selected limit** UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ adopted the long-term ESL of 0.001 g/m^3 for sodium oxalate from the NIOSH/OSHA/ACGIH 8 hr occupational exposure limit for oxalic acid of 1 mg/m^3 with a safety factor of 1000 (TCEQ, 2021). ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 1 mg/m^3 for oxalic acid. Leung and Paustenbach (1990) examined the irritancy potential for several carboxylic acids by studying the correlation between TLV-TWA values and acid dissociation constants, given that acidity is considered to be the principal factor in the irritancy potential for many carboxylic acids. The acids examined typically have a TLV-TWA basis of upper respiratory and eye irritation. After plotting the TLV-TWA values for a range of carboxyclic acids, a model was used to determine the TLV-TWA of oxalic acid, which resulted in a TLV-TWA of 1.05 mg/m^3. The TLV-TWA of 1 mg/m^3 is intended to protect against eye, skin, and upper respiratory tract irritation (ACGIH, 2015).
GENOTOXICITY / MUTAGENICITY	Negative results for mutagenicity were shown for oxalic acid using the Ames test, with and without activation (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for sodium oxalate.
CARCINOGENICITY	There was no carcinogenicity information identified for sodium oxalate.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for sodium oxalate.
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.01 mg/m^3** is selected as it is based on the ACGIH limit with an additional uncertainty factor of 100. This uncertainty factor is considered appropriate given that the ACGIH limit is based on occupational exposure to oxalic acid. The toxicological basis is related to the correlation between acidity and irritation. As sodium oxalate is considered a neutral substance, the use of the ACGIH limit is a conservative assessment of potential risks.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2015. Oxalic Acid, Anhydrous and Dihydrate. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Disodium Oxalate. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/28038/7/7/2. Last updated in July 2021. Last accessed in October 2021.

	Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Sodium Oxalate was not listed under ATSDR or PubChem.*

E.3.20 SODIUM SULPHATE [Na_2SO_4; CAS# 7757-82-6]

ACUTE TOXICITY / IRRITATION

Acute exposure to sodium sulphate may result in gastrointestinal irritation and diarrhea (PubChem, 2021).

Based on ACGIH's toxicological review, acute exposure to sodium bisulfate may cause mild eye and respiratory responses based on medial reports for workers (ACGIH, 2001).

TCEQ identified an acute exposure limit for aluminium goethite based on meeting the National Ambient Air Quality Standards (NAAQS) for PM. This is because for species of limited concern, the determination of the individual species impacts is not required if a NAAQS analysis is completed for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).

CHRONIC TOXICITY

There was no chronic toxicity information identified for sodium sulphate.

Based on ECHA's toxicological review, no adverse effects were predicted from repeated dose studies with animals exposed to sodium sulphate through inhalation (ECHA, 2021).

Based on ACGIH's toxicological review, inhalation exposure data either from experimental animal studies or occupational exposure of workers is not available (ACGIH, 2001).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	**5 mg/m^3**	**Eye, skin, mucous membrane, and respiratory tract irritation**	**Not specified**		**ACGIH (2001)** *Surrogated to sodium bisulfate*
TCEQ	Must meet NAAQS	-	-	-	TCEQ (2021) *Surrogated to PM*

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

American Conference of Governmental Industrial Hygienists (ACGIH)

ACGIH derived a TLV-TWA-TWA of 5 mg/m^3 for sodium bisulfate (used as a surrogate for sodium sulphate). The basis for deriving the TLV-TWA was not provided; however, it was

	recommended that a TLV-TWA of 5 mg/m^3 be adopted to minimize the potential for eye, skin, mucous membrane, and respiratory tract irritation (ACGIH, 2001). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ identified a chronic exposure limit for sodium sulphate based on meeting the NAAQS for $PM_{2.5}$ and PM_{10} (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	Based on the results of *in vitro* genetic toxicity studies, sodium sulphate is found to be non-mutagenic (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	The available data give no indication that sodium sulfate is toxic for reproduction. Developmental toxicity is unlikely given its natural occurrence in the body. Sodium sulphate should not be classified for reproduction and developmental toxicity (ECHA, 2021).
CARCINOGENICITY	Sodium sulphate is not classifiable as a human carcinogen (PubChem, 2021).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for sodium sulphate.
SELECTED EXPOSURE LIMIT	The ACGIH limit of 5 mg/m^3 is selected for sodium sulphate based on sodium bisulphate that is applied as a surrogate. An additional uncertainty factor of 1000 was applied based on the limited details on the supporting study of the ACGIH limit for sodium bisulphate applied as a surrogate for sodium sulphate, and to ensure protection of the general public including sensitive individuals from continuous exposures. The resulting adjusted exposure limit of **0.005 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Sodium Bisulfate. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Sodium Sulphate. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15539/7/13. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 24436, Sodium sulfate" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-sulfate. Last updated in October 2021. Last accessed in October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Sodium sulphate was not listed under ATSDR.*

E.3.21 STRONTIUM OXIDE [SrO; CAS#1314-11-0]

ACUTE TOXICITY / IRRITATION

Strontium oxide is classified as corrosive to the skin (Category 1B) and damaging to the eye (Category 1) (ECHA, 2021).

No acute exposure limits protective of inhalation of strontium were identified.

CHRONIC TOXICITY

Based on ATSDR's toxicological review, the only report of adverse respiratory effects in humans resulting from the inhalation of stable strontium is a case report of an anaphylactic reaction to smoke from an ignited roadside flare. The anaphylactic reaction to the smoke included coughing, wheezing, and severe respiratory difficulties. No other reports were located describing longer-term respiratory effects following inhalation of stable strontium compounds by humans or animals (ATSDR, 2004)

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	0.83 mg/m^3 (workers) 0.2 mg/m^3 (general public)	Thyroid weights increasement	Oral	-	ECHA (2021)
ACGIH	-	-	-	-	-
TCEQ	**0.005 mg/m^3**	-	-	-	**TCEQ (2021)** ***Surrogated to general ESL for metals with low toxicity***

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

European Chemical Agency (ECHA)

ECHA REACH identified chronic exposure limits for inhalation of strontium derived from route-to-route extrapolation based on an oral exposure study (ECHA, 2021).

Texas Commission on Environmental Quality (TCEQ)

TCEQ adopted a long-term ESL of 0.005 mg/m^3 of strontium oxide based on the general ESL for metals with low toxicity (TCEQ, 2021).

GENOTOXICITY / MUTAGENICITY

Strontium oxide is not expected to be genotoxic. Given the moiety, strontium has not shown gene mutation potential in bacteria and mammalian cells (ECHA, 2021).

REPRODUCTIVE / DEVELOPMENTAL TOXICITY

There was no reproductive/developmental toxicity information identified for strontium from inhalation exposure.

CARCINOGENICITY	Based on ATSDR's toxicological review, the only stable strontium compound that may cause cancer is strontium chromate, but this is due to chromium not strontium (ATSDR, 2004).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulation information identified for strontium from inhalation exposure.
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.005 mg/m^3** is selected for strontium oxide based on the general ESL for metals with low toxicity (TCEQ, 2021).
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological Profile for Strontium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Strontium Oxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/25528/7/9/1. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Strontium oxide was not listed under ACGIH, or PubChem.*

E.3.22 THORIUM OXIDE [ThO; CAS#1314-20-1]

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for thorium oxide or thorium. No acute exposure limits protective of inhalation of thorium were identified.
CHRONIC TOXICITY	Studies on thorium workers have shown that breathing dust containing thorium and other substances may damage the lung many years after being exposed. Sufficiently high exposure may also change the genetic material of cells where the thorium is deposited. One study showed that working in a thorium plant increased the chance of death in males; however, decreased the chance of death in females. Increasing the amount of thorium in your environment could increase your exposure to radium and radon. Therefore, it has not been determined whether the adverse health effects associated with exposure to thorium are the result of the ionizing radiation, the chemical toxicity of thorium, or a combination of radiation and chemical toxicity(ATSDR, 2019). No chronic exposure limits protective of inhalation of thorium were identified.
GENOTOXICITY / MUTAGENICITY	Based on the limited human data, thorium appears to be a genotoxic agent (ATSDR, 2019).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Based on ATSDR's toxicological review, thorium is not known to cause birth defects or to affect the ability to have children (ATSDR, 1990).

CARCINOGENICITY	Based on ATSDR's toxicological review, thorium was once thought to have caused cancer in mine and mill workers, but it was later concluded that thorium likely had no significant impact on their cancer risk. Cancers in those workers were likely due to their cigarette smoking and inhaling silica dust. Thorium is mildly radioactive (has a very long half-life) so health effects from exposure may be partly from the chemical itself and partly from the radiation it emits. IARC has not found sufficient evidence to classify thorium in mines and mills as carcinogenic. The National Toxicity Program (NTP) considers that thorium dioxide can cause cancer if it is injected into the body, as in medical procedure rather than inhaled. The carcinogenicity of thorium has not been evaluated in laboratory animals following inhalation (ATSDR, 2019).
SENSITIVE SUBPOPULATIONS	No sensitive subpopulations were identified for thorium oxide or thorium.
SELECTED EXPOSURE LIMIT	WSP applied the TCEQ long-term ESL **0.005 mg/m^3** used as the general ESL for metals with low toxicity for thorium oxide.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Toxicological profile for Thorium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. National Center for Biotechnology Information. "PubChem Compound Summary for CID 14808, Thorium dioxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Thorium-dioxide. Accessed 13 October, 2021. **Thorium oxide was not listed under ACGIH, ECHA, or TCEQ.*

E.3.23 VANADIUM PENTOXIDE [V_2O_5; CAS#1314-62-1]

ACUTE TOXICITY / IRRITATION	The main signs and symptoms of acute toxicity caused by single doses of the order of 100 mg of vanadium pentoxide included nausea, vomiting, salivation, and lacrimation, disappearance of pulse, and cylindrical casts and albumin in the urine. Men exposed to vanadium pentoxide while cleaning oil-fired burners or gas-fired turbines had symptoms consisting of cough, wheezing, rhinitis, sneezing, nosebleeds, sore throat, fatigue, nervousness, eye irritation, hoarseness, and chest pain. Workers exposed to vanadium pentoxide for only a few days may develop irritation of the conjunctivae, rhinitis, dryness of the throat, hoarseness, bronchitis with coughing and wheezing, dyspnea, and pneumonitis. A green-black discoloration of the tongue sometimes occurs. (PubChem, 2021) Exposure to high levels of vanadium pentoxide in air can result in lung damage. Nausea, mild diarrhea, and stomach cramps have been reported in people from acute exposure to some vanadium compounds. (ATSDR, 2012). According to the review conducted by ECHA, vanadium pentoxide is not a skin irritant but it is considered to be damaging to eyes (ECHA, 2021). TCEQ developed an acute (1 hr) AMCV for vanadium pentoxide of 3.3 µg/m^3. The AMCV was derived from Zenz and Berg (1967), a human study where 9 healthy male volunteers (age 27-44

years) were exposed to 0.1, 0.25 or 1.0 mg/m³ of respirable V_2O_5 dust (particle size: 98% < 5 µm) for 8 hours. The NOAEL of 0.1 mg/m³ was selected as the point of departure (POD) based on respiratory irritation. The POD was adjusted for a 1 hr exposure concentration. An uncertainty factor (UF) of 10 was applied to account for variation in susceptibility among members of the human population to sensory irritation, and a database UF of 6 because only one human and 2 animal studies are available to support the value. An acute (1 hr) ESL of 1 µg/m³ was calculated from the AMCV based on a target hazard quotient of 0.3 (TCEQ, 2021).

ECHA REACH provide acute limits for vanadium pentoxide of 0.7 mg/m³ for workers and 0.45 mg/m³ for the general public protective of nasal irritation. However, there was no further information available on the primary study and derivation of these values (ECHA, 2021).

CHRONIC TOXICITY

Based on ATSDR's toxicological review, chronic inhalation exposure to vanadium may cause asthma and may make vanadium workers more susceptible to colds and other respiratory illnesses. Exposure to vanadium may impair the lung resistance to respiratory infection (PubChem, 2021).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	0.5 mg/m³ (systemic-worker) 0.14 mg/m³ (local- worker) 0.14 mg/m³ (systemic- public) 0.09 mg/m³ (local- public)	Systemic: developmental toxicity, teratogenicity Local: nasal irritation	Not specified-	-	ECHA (2021)
ACGIH	**0.05 mg/m³**	**Upper and lower respiratory tract irritation**	**Chronic - human (Kiciluote, 1979)**		**ACGIH (2009)**
TCEQ	0.0003 mg/m³	Asthma	Acute - human (Zenz and Berg, 1967)	Safety factor of 10 applied to the short-term AMCV.	TCEQ (2021)

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

European Chemical Agency (ECHA)

ECHA provide chronic exposure limits for vanadium pentoxide of 0.5 mg/m³ (for systemic effects) and 0.14 mg/m³ (for local effects) for workers and 0.14 mg/m³ (for systemic effects) and 0.09 mg/m³ (for local effects) for the general public. These limits are based on the protection of developmental toxicity / teratogenicity for systemic effects and nasal irritation for local

	effects. However, there was no further information available on the primary study and derivation of these values (ECHA, 2021). ***American Conference of Governmental Industrial Hygienists (ACGIH).*** ACGIH identified a TLV- TWA of 0.05 mg/m^3 for vanadium pentoxide. The TLV-TWA was based on human data from Kiviluoto (1979). The study showed that subjects exposed to 0.2-0.5 mg V/m^3 measured as total dust for 11 years in the vanadium industry did not develop any upper respiratory symptoms, but did show increased leuocytes (from nasal biopsy results) and self reported wheezing when compared to a referent group. The differences in nasal biopsy results were resolved after exposure was reduced to 0.01 to 0.04 mg V/m^3 as total dust. The study supports a TLV-TWA of 0.02 to 0.08 mg/m^3 (adjusted inhalable) that is not associated with nasal changes. A TLV-TWA of 0.05 mg/m^3 represents the adjusted mean of the no effect range considered to be protective of airway inflammatory changes from exposure to vanadium pentoxide (ACGIH, 2009). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ developed a long-term AMCV for vanadium pentoxide of 0.3 µg/m^3 by applying a safety factor of 10 to the short-term AMCV (TCEQ, 2021). The basis of the short term AMCV is discussed under the "Acute Toxicity" section.
GENOTOXICITY / MUTAGENICITY	The weight-of-evidence of the entire genotoxicity database does not show any clear evidence of germ cell mutagenicity from vanadium pentoxide (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Information on the potential of vanadium to induce developmental effects in humans is limited, but developmental effects have been observed in laboratory animals. Decreases in pup growth have been observed at maternal oral doses of ≥2.1 mg vanadium/kg/day. At higher doses, decreases in pup survival and gross, skeletal, and visceral malformations and anomalies have been reported; marked decreases in maternal body weight are also observed at these dose levels (ATSDR, 2012).
CARCINOGENICITY	The IARC has classified vanadium pentoxide as possibly carcinogenic to humans based on evidence of lung cancer in exposed mice (ATSDR, 2012).
SENSITIVE SUBPOPULATIONS	Health effects in children are expected to be similar to the effects seen in adults. Studies in animals exposed during pregnancy have shown that vanadium can cause decreases in growth and increases in the occurrence of birth defects (ATSDR, 2012).
SELECTED EXPOSURE LIMITS	The ACGIH limit of 0.05 mg/m^3 is selected for vanadium pentoxide based on chronic exposure to humans. The TCEQ limit is based on acute exposure to humans. An additional uncertainty factor of 100 was applied to ensure protection of the general public including sensitive individuals such as children, asthmatics and elderly from continuous exposures. The resulting adjusted exposure limit of **0.0005 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological Profile for Vanadium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

	American Conference of Governmental Industrial Hygienists (ACGIH). 2009. Vanadium Pentoxide. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Divanadium pentaoxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15418/7/9/1. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 14814, Vanadium pentoxide" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Vanadium-pentoxide.Last updated in October 2021. Last accessed in October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. Interim 1-h Reference Value and Short- and Long-term Effects Screening Levels for Vanadium Pentoxide and Vanadium Compounds.

E.3.24 YTTRIUM TRIOXIDE [Y_2O_3; CAS#1314-36-9]

ACUTE TOXICITY / IRRITATION	Based on ACGIH's toxicological review, acute exposure to yttrium may cause mild irritation of the eyes, upper respiratory passages, and skin (ACGIH, 2001). ECHA (2021) also identified yttrium oxide as slightly irritating to the eyes. TCEQ adopted the short-term ESL for a one hour exposure period of 10 µg/m^3 from the NIOSH/OSHA/ACGIH 8-hr TWA for yttrium of 1 mg/m^3 with a safety factor of 100 (TCEQ, 2021).
CHRONIC TOXICITY	Based on ACGIH's toxicological review, the occupational studies of chronic exposure to yttrium failed to show effects attributable to the yttrium (ACGIH, 2001). As part of ECHA REACH, a chronic toxicity study looking at the effects from inhalation of yttium trioxide in animals established a NOAEL above 20.63 mg/m^3. The observed effects were consistent with a local inflammatory response of lung function following inhalation of poorly soluble particles of low toxicity, with no systemic effects and a limited relevance to the human occupational situation given the exposure levels. Based on this, a chronic exposure limit ws not developed by the ECHA (ECHA, 2021). Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-		ECHA (2021)
ACGIH	**1 mg/m^3**	**Respiratory fibrosis**	**Acute – animal (Mogilevskaya & Raikhlin., 1963)**		**ACGIH (2001)**
TCEQ	0.001 mg/m^3	-	Adopted from ACGIH value	Safety factor of 1000 applied by TCEQ	TCEQ (2021)

	Notes: **Bold = selected limit** UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 1 mg/m^3 for yttrium and its compounds. The TLV-TWA value is intended to protect against respiratory fibrosis, as reported in rats by Mogilevskaya O.Y and Rakhlin N.T (1963).The study administered a single 50 mg dose of yttrium intratracheally to rats and sacrificed the animals 8 months later. The rats developed pulmonary changes, including increased lung weight, diffuse fibrosis, and emphysema. No further information was available as to how the TLV-TWA was derived from this study (ACGIH, 2001). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ adopted the long-term ESL of 1 µg/m^3 from the NIOSH/OSHA/ACGIH 8 hr TWA for yttrium of 1 mg/m^3 with a safety factor of 1000 (TCEQ, 2021).
GENOTOXICITY / MUTAGENICITY	Reverse gene mutation assays in bacteria, mammalian cell gene mutation assays *in vitro*, and chromosomal aberration *in vitro* in human lymphocytes all reported negative results suggesting that yttrium oxide is not genotoxic (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified related to inhalation exposures. Animal studies examining the oral toxicity of yttrium oxide did not report any toxicologically relevant findings for reproductive and developmental parameters (ECHA, 2021).
CARCINOGENICITY	There was no carcinogenicity information identified for yttrium trioxide.
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for yttrium trioxide.
SELECTED EXPOSURE LIMIT	The ACGIH limit of 1 mg/m^3 was selected for yttrium trioxide given that TCEQ limit is adopted from ACGIH TLV-TWA. An additional uncertainty factor of 1000 was applied to account for acute to chronic uncertainty, animal to human uncertainty, and to ensure protection of the general public including sensitive individuals from continuous exposures. The resulting adjusted exposure limit of **0.001 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Yttrium and Compounds. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Yttrium Oxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14370/7/1. Last updated in July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021.

	**Yttrium trioxide was not listed under ATSDR or PubChem.*

E.3.25 ZINC OXIDE [ZnO; CAS#1314-13-2]

ACUTE TOXICITY / IRRITATION

Based on ATSDR's toxicological review, acute inhalation of large amounts of zinc oxide dusts may cause metal fume fever. Metal fume fever is characterized by chest pain, cough, dyspnea, reduced lung volumes, nausea, chills, malaise, and leukocytosis. Symptoms generally appear a few hours after exposure, and are reversible 1–4 days following cessation of exposure. Exposure levels associated with the development of metal fume fever are generally in the range of 77–600 mg zinc/m^3 · Occupational exposures to low concentrations of zinc (8–12 mg zinc/m^3 for 1–3 hours and 0.034 mg zinc/m^3 for 6–8 hours) did not produce symptoms of metal fume fever. (ACGIH, 2003 and ATSDR, 2005).

ACGIH derived a TLV-STEL of 10 mg/m^3 for zinc oxide based on controlled clinical exposures that demonstrated a significant pulmonary response occurs after a brief exposure to high levels of zinc oxide (greater than 10 mg/m^3) (ACGIH, 2003).

TCEQ adopted the short-term ESL for a one hour exposure period for zinc oxide of 24 µg/m^3 from the German MAK of 2.4 mg/m^3 with an additional safety factor of 100 (TCEQ, 2021).

CHRONIC TOXICITY

Based on ATSDR's toxicological review, there were no chronic inhalation studies identified for zinc oxide (ATSDR, 2005).

Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	0.5 mg/m^3 (workers)	Changes to bronchoalveolar lavage fluid	Subchronic - animal (OECD Guideline 408& 413)	$UF_H = 3$	ECHA (2021)
ACGIH	2 mg/m^3 (respirable particulate mass)	Metal fume fever	Acute- human (Fine *et al.*, 1997)	-	ACGIH (2003)
TCEQ	**0.0024 mg/m^3**	**Lung function disorders; asthmatic symptoms**	**Chronic – human** (Roto, 1980)	**Safety factor =1000**	**TCEQ (2021)** *Adopted from German MAK*

Notes:

Bold = selected limit

UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty)

European Chemical Agency (ECHA)

	ECHA developed a chronic exposure limit for workers exposed to zinc oxide of 0.5 mg/m^3 based on a 90-day repeated dose inhalation toxicity study (OECD Guideline 413). Male rats were exposed to concentrations of nanoscale zinc oxide at 0.3, 1.5 and 4.5 mg/m^3 through the nose. The NOAEL was determined to be 1.5 mg/m^3 based on changes to the broncho-alveolar lavage (BAL). An uncertainty factor of 3 was applied to account for intraspecies differences. Exposure limits were also derived for the protection of systemic effects (reduced ESOD activity); however, these were derived from route-to-route extrapolation from oral exposure studies and are no longer considered (ECHA, 2021). ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 2 mg/m^3 for zinc oxide. The TLV-TWA is based on Fine *et al.* (1997), who performed a series of studies in which they found that metal fume fever can occur in humans after a 2-hour exposure at 2.5 mg/m^3 of freshly formed zinc oxide. However, these investigators also reported in follow-up studies (2000) that sheet metal workers exposed to 5 mg/m^3 of zinc oxide for 2-hrs for 3 days did not develop metal fume fever. At 2 mg/m^3, it is considered that the incidence of metal fume fever will be low and the cases that may occur will be mild (ACGIH, 2003). ***Texas Commission on Environmental Quality (TCEQ)*** TCEQ adopted the long-term ESL/AMCV of 2.4 $\mu g/m^3$ for zinc oxide based on the German MAK for zinc of 2.4 mg/m^3 with an additional safety factor of 1000 (TCEQ, 2021). The MAK value was derived based on Roto (1980), an occupational study where 234 zinc ore smelting workers were exposed to 2.5 to 4.5 mg/m^3 of zinc oxide (as total dust with 90% zinc content) for an average of 5.5 years. No effects related to lung function disorders or asthmatic symptoms were observed across exposure groups. The NOAEL of 2.5 mg/m^3 was selected as the point of departure (POD) (DFG, 2014).
GENOTOXICITY / MUTAGENICITY	Based on the ECHA toxicological review, there was mutagenic or genotoxic effects observed from *in vitro* bacterial assays and *in vivo* inhalation rat studies with zinc oxide (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Based on ATSDR's toxicological review, available studies have not presented evidence of reproductive or developmental effects in humans or animals following inhalation of zinc compounds. Effects on reproductive or developmental end points have been noted in oral-exposure animal studies, but generally only at very high doses (>200 mg/kg/day) (ATSDR, 2005).
CARCINOGENICITY	Zinc is not classifiable as to its human carcinogenicity due to inadequate human and animal studies (ECHA, 2021 and ATSDR, 2005).
SENSITIVE SUBPOPULATIONS	Based on ATSDR's toxicological review, it is unknown if children are more susceptible to effects from zinc than adults or if zinc causes developmental effects in humans. Animal studies have found decreased weight in the offspring of animals that ingested very high amounts of zinc (ATSDR, 2005).
SELECTED EXPOSURE LIMIT	The TCEQ limit of **0.0024 mg/m^3** is selected for zinc oxide based on a chronic occupational exposure study and adjusted by an uncertainty factor of 1000 to be protective of the general population including sensitive individuals.

REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Toxicological Profile for Zinc (Update). Atlanta, GA: U.S. Department of Public Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2003. Zinc Oxide. Deutsche For schungsgemeinschaft (DFG). 2014. The MAK-Collection Part I, MAK Value Documentations 2014. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Zinc Oxide. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/16139/7/9/2. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. 2021. PubChem Compound Summary for CID 14806, Zinc Oxide. Accessed online at: https://pubchem.ncbi.nlm.nih.gov/compound/Zinc-oxide. Last updated in October 2021. Last accessed in October, 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021.

APP

E.3.26 ZIRCON [$ZrSiO_4$; CAS# 10101-52-7]

**Also known as Zirconium Silicate*

ACUTE TOXICITY / IRRITATION	There was no acute toxicity information identified for zircon. Based on ACGIH's toxicological review, acute inhalation exposures to zirconium may cause progressive depression until death for the animals (ACGIH, 2001).
CHRONIC TOXICITY	There was no chronic toxicity information identified for zircon. Based on ACGIH's toxicological review, chronic inhalation exposures to zirconium fume by workers for 1 to 5 years revealed no abnormalities (ACGIH, 2001). Inhalation exposure limits protective of chronic health are summarized below:

AGENCY	VALUE	HEALTH ENDPOINT	STUDY TYPE	UF	SOURCE
ECHA	-	-	-	-	ECHA (2021)
ACGIH	**5 mg/m^3**	**Respiratory irritation**	**Chronic – animal (Stokinger H.E, 1981; Hodge H.C, 1955)**		**ACGIH (2001)**
TCEQ	-	-	-	-	TCEQ (2021)

Notes:

Bold = selected limit

	UF = uncertainty factor; UF_H (for intraspecies human uncertainty); UF_A (for animal to human uncertainty); UF_{sub} (for subchronic to chronic uncertainty); UF_L (for LOAEL to NOAEL uncertainty); UF_D (for incomplete database uncertainty) ***American Conference of Governmental Industrial Hygienists (ACGIH)*** ACGIH derived a TLV-TWA of 5 mg/m^3 for zirconium and its compounds (including zirconium silicate). The TLV-TWA is based on several studies. An animal inhalation study by Spiegl *et al.* (1956), where exposure to zirconium tetrachloride at a concentration of 6 mg Zr/m^3 for two months was associated with a small increase in mortality of rats and guinea pigs and no increased mortality for rabbits, cats or dogs. Respiratory infection was the cause of death. Also, two 1-yr animal inhalation studies (Stokinger H.E, 1981; Hodge H.C, 1955) where exposure to zirconium tetrachloride at 3.5 mg/m^3 resulted in no adverse effects. The TLV- TWA of 5 mg/m^3 is intended to protect against respiratory irritation (ACGIH, 2001).
GENOTOXICITY / MUTAGENICITY	There was no genotoxicity/mutagenicity information identified for zircon or zirconium.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no reproductive/developmental toxicity information identified for zircon or zirconium.
CARCINOGENICITY	There was no carcinogenicity information identified for zircon. Zirconium and its compounds were not classified as a human carcinogen (ACGIH, 2001).
SENSITIVE SUBPOPULATIONS	There was no sensitive subpopulations information identified for zircon or zirconium.
SELECTED EXPOSURE LIMIT	The ACGIH limit of 5 mg/m^3 was selected for zirconium. An additional uncertainty factor of 1000 was applied to the ACGIH limit to account for animal to human uncertainty and to ensure protection of the general public including sensitive individuals namely children, asthmatics and elderly from continuous exposures. The resulting adjusted exposure limit of **0.005 mg/m^3** is applied in the quantitative risk analysis.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Zirconium and Compounds. **Zircon was not listed under ATSDR, ECHA, PubChem, or TCEQ.*

E.4 TOXICITY PROFILES FOR GRAS PARAMETERS

E.4.1 BACKGROUND

There were several constituents of bauxite residue and salt cake that were screened out from further evaluation in the HHA on the basis that they were listed as "Generally Recognized as Safe" ("GRAS") by the US Food and Drug Administration (FDA). Those substances listed as Type 1 by US FDA have been concluded to have no evidence that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future (US FDA, 2018). The constituents of bauxite residue and salt cake that were not further assessed in this HHA include:

- Bayer Sodalite
- Gibbsite
- Quartz
- Sodium Carbonate
- Carbonate Apatite
- Sodium Bicarbonate
- Sodium Aluminate
- Sodium Hydroxide
- Magnesium Oxide
- Potassium Carbonate

Toxicity profiles for these parameters are provided below.

E.4.2 BAYER SODALITE [$3(Na_2O.Al_2O_3{\cdot}2SiO_2.2H_2O){\cdot}0.8Na_2CO_3{\cdot}0.2Na_2SO_4$; CAS#1344-00-9]

ACUTE TOXICITY / IRRITATION	As there was no toxicity data related to synthetic amorphous aluminum sodium silicate (NAS), experimental data from structure-analogous silicas (SAS) was summarised for ECHA REACH. All acute inhalation studies performed with dry dust of SAS were hampered by the technical problem to achieve the recommended highest test concentration of 5 mg/L. This is because of the high adhesive forces which caused rapid precipitation onto equipment walls. Therefore, the maximum attainable chamber concentrations were distinctly lower (ECHA, 2021).
CHRONIC TOXICITY	As there was no toxicity data related to NAS, experimental data from SAS was summarized for ECHA REACH including a sub-chronic inhalation study (Degussa 1987). Thirteen-weeks of inhalation exposure to an average concentration of 1.3 mg/m^3 of a pyrogenic SAS resulted in mild reversible pro-inflammatory cell proliferation rather than a pathologically relevant tissue change (identified as the NOAEL). The LOAEL was 5.9 mg/m^3, the mid concentration, which produced clear signs of histopathological adverse effects (stimulation of collagen production, increase in lung weight, incipient interstitial fibrosis in the lung, slight focal atrophy in the olfactory epithelium). All these effects were reversible following discontinuation of exposure. The low exposure level did not provide any evidence of an accumulation of adverse effects over time (ECHA, 2021).
GENOTOXICITY / MUTAGENICITY	NAS gave no evidence of a mutagenic potential in various in-vitro and in-vivo studies, additionally supported by negative results obtained with structure-analogous silica and silicate (ECHA, 2021)
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	There was no adverse maternal and embryo-/feto- toxic effects in four species exposed to NAS (mouse, rat, rabbit and hamster) following doses of up to 1600 mg/(kg bw*d) during gestation (ECHA, 2021). No inhalation exposure studies were identified.

CARCINOGENICITY	No carcinogenic effects were observed with NAS in a rat carcinogenicity model after intra-pleural treatment, as well as in a long-term feeding study with structure-analogous silica in mice and rats (ECHA, 2021).
SENSITIVE SUBPOPULATIONS	No sensitive subpopulations were identified.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Silicic acid, aluminum sodium salt. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15116. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 19758701, Sodium aluminosilicate". Accessed online at: https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-aluminosilicate. Last updated in October 2021. Last accessed October 2021. **Bayer solidate was not listed under ACGIH, ATSDR, PubChem or TCEQ.*

E.4.3 CARBONATE APATITE [$5.2CaO \cdot 0.8Na_2O \cdot 2.5CO_2 \cdot P_2O_5$; CAS#471-34-1]

**Also known as Calcium Carbonate*

ACUTE TOXICITY / IRRITATION	Carbonate apatite may cause mechanical irritation to the respiratory tract and eyes (PubChem, 2021).
CHRONIC TOXICITY	According to the summary from PubChem, chronic health effects of from carbonate apatite exposures have been investigated but none have been found (PubChem, 2021).
GENOTOXICITY / MUTAGENICITY	Several *in vitro* experiments have showed that, uncoated nano calcium carbonate was negative for genotoxicity and mutagenicity (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Not identified.
CARCINOGENICITY	Not identified.
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Calcium Carbonate. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16050/7/8 . Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 10112, Calcium carbonate". Accessed online at:

	https://pubchem.ncbi.nlm.nih.gov/compound/Calcium-carbonate. Last updated in October 2021. Last accessed in October 2021. **Carbonate apatite was not listed under ATSDR, ACGIH or TCEQ.*

E.4.4 GIBBSITE [$Al_2O_3.3H_2O$; CAS#21645-51-2]

**Also known as Aluminum Hydroxide*

ACUTE TOXICITY / IRRITATION	As part of ECHA, an acute study was completed for aluminium hydroxide. Mortality occurred either during or shortly after exposure and the clinical symptoms observed were consistent with respiratory distress. A slight (otherwise unspecified) effect on weight gain was reported. The surviving animals were described as showing only "slight" toxic effects and good recovery by the end of the 14 day observation period. A greater amount of discolouration was observed on the surface of lungs of treated animals compared with control animals. A "slight" increase in the number of lesions on the lungs of the test animals was also reported – although individual data or further detailed was not provided. The LC50 estimated from this study based on only one hour of exposure was 7.6 mg/L (95% CI: 6.45 – 8.95 mg/L) (ECHA, 2021).
CHRONIC TOXICITY	As part of ECHA REACH for aluminum hydroxide, a sub-chronic study was completed with aluminium dust (Ess et al., 1993). The test materials were five fine alumina dusts obtained from sieving raw alumina samples (Dusts 1 to 5), a chemical grade alumina (Dust 6) and an alumina produced in the laboratory (Dust 7). Two experiments were conducted; one in female rats with administration by intratracheal instillation and the other in male mice with administration of the dusts by intraperitoneal injection. In the rat study, a total dose of 50 mg was administered as dust over a two-week period. In the mice study, they were injected with a 0.5 mL volume of 1% suspension of dust in sterile isotonic saline. Overall, all dust samples produced an inflammatory alveolar reaction on intratracheal instillation at these doses. The smelter-grade dusts did not show evidence for a fibrotic effect in the rats' lungs during the period of a year following intratracheal instillation. In contrast, the chemical grade, ultrafine non-alpha alumina and dust and the laboratory grade alumina showed evidence of definite fibrotic changes. The results clearly show the importance of the physical characteristics of the alumina dust on the biological response (ECHA, 2021).
GENOTOXICITY / MUTAGENICITY	The weight of evidence for aluminium compounds does not support a systemic mutagenic hazard for aluminium hydroxide (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	The effects of inhaled aluminium metal, aluminium oxide and aluminium hydroxide on reproductive/developmental outcomes have not been investigated directly in epidemiological studies (ECHA, 2021)
CARCINOGENICITY	The weight of evidence does not support a systemic carcinogenic effect from exposure to aluminium hydroxide. The weight of evidence also does not support a local carcinogenic effect from exposure to aluminium hydroxide. (ECHA, 2021).
SENSITIVE SUBPOPULATIONS	Not identified.

REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Aluminum Hydroxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15529/7/8. Last updated July 2021. Last accessed in October 2021. Texas Commission on Environmental Quality (TCEQ). 2021. TAMIS Tox-ESL Summary Report. Last accessed in October 2021. **Gibbsite was not listed under ATSDR, ACGIH or PubChem.*

E.4.5 MAGNESIUM OXIDE [MgO; CAS#1309-48-4]

ACUTE TOXICITY / IRRITATION	Human studies have shown that acute exposure to magnesium oxide through inhalation can cause localized respiratory irritation (conjunctivitis, nasal catarrh, and coughing up discolored sputum) and metal fume fever (febrile reaction and a leukocytosis) (PubChem, 2021).
CHRONIC TOXICITY	No chronic toxicity studies for magnesium oxide were identified (PubChem, 2021)
GENOTOXICITY / MUTAGENICITY	Not identified.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Not identified.
CARCINOGENICITY	Magnesium oxide is not classifiable as a human carcinogen (PubChem, 2021).
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2003. Magnesium Oxide. National Center for Biotechnology Information. "PubChem Compound Summary for CID 14792, Magnesium oxide". Online access at: https://pubchem.ncbi.nlm.nih.gov/compound/Magnesium-oxide. Last updated October 2021. Last accessed October 2021. **Magnesium oxide was not listed under ATSDR, ECHA, or TCEQ.*

E.4.6 POTASSIUM CARBONATE [K_2CO_3; CAS#584-08-7]

ACUTE TOXICITY / IRRITATION	As part of ECHA REACH, an acute inhalation toxicity study completed on rats exposed to potassium carbonate for 4.5 hours identified an LC50 greater than 4.96 mg/L. The rats experienced decreased activity, irregular respiration, hunched posture, lethargy and irritation within 24 hours of exposure. Dermal necrosis around the mouth and corneal opacity were noted in all animals. Most animals recovered by day 6 and there was no necropsy identified. As no animal died, potassium carbonate was not classified as acutely toxic from inhalation according to CLP, EU GHS (Regulation (EC) No 1272/2008) (ECHA, 2021).
CHRONIC TOXICITY	As part of ECHA REACH, a chronic inhalation toxicity study completed on rats exposed to potassium carbonate for 6 h/d for 21 consecutive days identified a NOAEC of 0.12 mg/L in air based on the lowest exposure concentration. The exposure did not result in any relevant systemic toxicity or neurotoxicity in either male or female rats. Reversible histopathological changes were noted in the nasal cavities and in the lungs. The alkalinity of the material was determined to cause the respiratory irritation (ECHA, 2021).
GENOTOXICITY / MUTAGENICITY	Based on the toxicological review provided by the ECHA, there is no evidence for potassium carbonate resulting in genotoxic activity to humans based on *in vitro* studies in bacteria and mammalian cells (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Based on the toxicological review provided by the ECHA, there are no indications of reproductive or developmental toxicity from potassium carbonate. Further, no reproductive toxicity is expected to occur because potassium carbonate will not affect the natural K^+ or CO_3^{2-} levels in the body and will not reach the foetus nor reach male and female reproductive organs (ECHA, 2021)
CARCINOGENICITY	Based on the toxicological review provided by the ECHA, there are no reliable studies on the carcinogenicity of potassium carbonate. Reliable oral studies on related potassium hydrogen carbonate substances do not show evidence of carcinogenicity to humans. Finally, OECD assessments on high production volume chemicals which have a carbonate or a potassium moiety have also not shown carcinogenic effects (ECHA, 2021)
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Potassium Carbonate. Accessed online at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15221/7/8. Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. PubChem Compound Summary for CID 11430, Potassium Carbonate. Online access at: https://pubchem.ncbi.nlm.nih.gov/compound/Potassium-carbonate. Last updated in October 2021. Last accessed in October 2021. **Potassium carbonate was not listed under ATSDR, ACGIH, or TCEQ.*

E.4.7 QUARTZ [SiO_2; CAS#14808-60-7]

**Also known as Silica or Silicon Dioxide`*

ACUTE TOXICITY / IRRITATION	In a study by Warheir et al. (1991), rats were exposed to 10, 50, and 100 mg/m^3 silica as quartz for 6 h. The 10 mg/m^3 exposure level was selected as the LOAEL, based on respiratory inflammation–increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid in rats (male).
CHRONIC TOXICITY	Silicosis, lung cancer and pulmonary tuberculosis are associated with occupational exposure to quartz dust. Statistically significant increases in deaths or cases of bronchitis, emphysema, chronic obstructive pulmonary disease, autoimmune related diseases (scleroderma, rheumatoid arthritis, systemic lupus erythematosus) and renal diseases have also been reported (PubChem, 2021, TCEQ, 2013. ACGIH, 2010).
GENOTOXICITY / MUTAGENICITY	Not identified.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Not identified.
CARCINOGENICITY	Quartz is classified as suspected human carcinogen (PubChem, 2021).
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	American Conference of Governmental Industrial Hygienists (ACGIH). 2010. Silica, Crystalline - α Quartz and Cristobalite. National Center for Biotechnology Information. "PubChem Compound Summary for CID 24261, Silicon dioxide" Online access at: https://pubchem.ncbi.nlm.nih.gov/compound/Silicon-dioxide. Last updated October 2021. Last accessed October 2021. Texas Commission on Environmental Quality (TCEQ). 2013. Development Support Document for Silica, Crystalline Forms. **Quartz was not listed under ATSDR, ECHA, or PubChem.*

E.4.8 SODIUM ALUMINATE [$NaAl(OH)_4$; CAS#11138-49-1]

ACUTE TOXICITY / IRRITATION	According to the review conducted by PubChem, inhaled sodium aluminate may cause burning sensation, sore throat, cough, and laboured breathing (PubChem, 2021)
CHRONIC TOXICITY	No chronic toxicity information was identified for sodium aluminate.
GENOTOXICITY / MUTAGENICITY	Not identified.
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Not identified.
CARCINOGENICITY	Not identified.
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	National Center for Biotechnology Information. "PubChem Compound Summary for CID 14766, Sodium aluminate". Online access at: https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-aluminate. Last updated in October 2021. Last accessed October 2021. **Sodium aluminate was not listed under ACGIH, ATSDR, ECHA or TCEQ.*

E.4.9 SODIUM BICARBONATE [$NaHCO_3$; CAS# 144-55-8]

ACUTE TOXICITY / IRRITATION	No acute toxicity information was identified for sodium bicarbonate.
CHRONIC TOXICITY	No chronic toxicity information was identified for sodium bicarbonate.
GENOTOXICITY / MUTAGENICITY	Sodium bicarbonate is naturally present in cells and the structure does not indicate a genotoxic potential. Therefore, sodium bicarbonate is considered to be not genotoxic. Moreover, is the substance already present in the tissue culture media of the *in vitro* test systems for genetic toxicity testing and needed for normal function of the cells in culture. Testing sodium bicarbonate *in vitro* will affect the cellular homeostasis due to osmolarity and/or pH of the culture medium which might give rise to a specific effect (PubChem, 2021)
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Bulk calcium carbonate showed no signs of developmental toxicity in a prenatal developmental screening toxicity test (ECHA, 2021).
CARCINOGENICITY	Sodium bicarbonate is not classifiable as a human carcinogen (PubChem, 2021)
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Sodium bicarbonate. Accessed online at:

	https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16050/7/8 . Last updated in July 2021. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 516892, Sodium bicarbonate". Online access at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16157/7/1. Last updated October 2021. Last accessed October 2021. **Sodium bicarbonate was not listed under ACGIH, ATSDR or TCEQ.*

E.4.10 SODIUM CARBONATE [Na_2CO_3; CAS#497-19-8]

ACUTE TOXICITY / IRRITATION	Humans have been regularly exposed to sodium carbonate in various guises over a considerable length of time. There have been no significant reports of ill health caused by inhalation of sodium carbonate either in powder or aerosol form (ECHA, 2021).
CHRONIC TOXICITY	
GENOTOXICITY / MUTAGENICITY	The available *in vitro* tests (SOS chromotest with sodium carbonate and Ames test with sodium bicarbonate) were negative. Sodium bicarbonate is naturally present in cells and both the structure of sodium bicarbonate and sodium carbonate do not indicate a genotoxic potential. Therefore, there is no reason to evaluate the potential genotoxicity of sodium carbonate further and no genotoxic effects are expected (PubChem, 2021; ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Not identified.
CARCINOGENICITY	Not identified.
SENSITIVE SUBPOPULATIONS	Not identified.
REFERENCES	European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Sodium Carbonate. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15432/7/9/1. Last accessed in October 2021. National Center for Biotechnology Information. "PubChem Compound Summary for CID 10340, Sodium carbonate", online access at: https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-carbonate. Last updated November 2021. Last accessed November 2021. **Sodium carbonate was not listed under ACGIH, ATSDR, or TCEQ.*

E.4.11 SODIUM HYDROXIDE [NaOH; CAS#1310-73-2]

ACUTE TOXICITY / IRRITATION	Sodium hydroxide (NaOH) is very corrosive and can cause severe burns in all tissues that come in contact with it. Inhalation of low levels of sodium hydroxide as dusts, mists or aerosols may cause irritation of the nose, throat, and respiratory airways. Inhalation of higher levels can produce swelling or spasms of the upper airway leading to obstruction and loss of measurable pulse; inflammation of the lungs and accumulation of fluid in the lungs may also occur (ATSDR, 2002). Based on the ACGIH review, a human study examined the irritant effects of caustic mists encountered in concentrations of 1 to 40 mg/m^3. A concentration of 2 mg/m^3 was considered to produce noticeable, but not excessive, ocular and upper respiratory tract irritation. Several studies reported noticeable irritation at concentration of NaOH below 2 mg/m^3 (ACGIH, 2001).
CHRONIC TOXICITY	Long-term exposure to sodium hydroxide in the air may lead to ulceration of the nasal passages and chronic skin irritation (ATSDR, 2002).
GENOTOXICITY / MUTAGENICITY	Both *in vitro* and *in vivo* genetic toxicity tests indicated no evidence for mutagenic activity. Furthermore, NaOH is not expected to be systemically available in the body under normal handling and use conditions and for this reason additional testing is considered unnecessary (ECHA, 2021).
REPRODUCTIVE / DEVELOPMENTAL TOXICITY	Sodium hydroxide is not expected to be systemically available in the body under normal handling and use conditions and for this reason it was concluded that NaOH will not reach the foetus nor male and female reproductive organs. Therefore, a specific study to identify the potential for developmental or reproductive toxicity is not necessary (ECHA, 2021).
CARCINOGENICITY	Since NaOH is not expected to be systemically available in the body under normal handling and use conditions, systemic carcinogenicity is unlikely to occur. Additionally, no suitable studies are available to assess the risk on local carcinogenic effects (ECHA, 2021).
SENSITIVE SUBPOPULATIONS	There are no studies on the health effects of children exposed to sodium hydroxide. The effects seen in children accidently exposed to sodium hydroxide are similar to the effects observed in adults. It is unclear if exposure to sodium hydroxide can result in birth defects or other developmental effects in people. (ATSDR, 2002)
REFERENCES	Agency for Toxic Substances and Disease Registry (ATSDR). 2002. Managing Hazardous Materials Incidents. Volume III. Medical Management Guidelines for Acute Chemical Exposures: Sodium Hydroxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Sodium Hydroxide. European Chemical Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) for Sodium Hydroxide. Accessed online at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15566/7/3/3. Last updated in July 2021. Last accessed in October 2021.

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