Aluminum Diethylphosphinate (CAS #225789-38-8) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Clariant

Prepared by:

ToxServices LLC

October 31, 2016

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Aluminum Diethylphosphinate (CAS #225789-38-8)

Aluminum diethylphosphinate is an organophosphorus salt that functions as a flame retardant for engineering plastics such as polyamides, polyesters, and thermoset resins.

Aluminum diethylphosphinate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard score:

- Benchmark 3a
    - Very High Persistence-P

A data gap (DG) exists for endocrine activity-E. The lack of data for single exposure systemic toxicity-STs and single exposure neurotoxicity-Ns is not counted in the benchmarking process as data are available for repeated exposure systemic toxicity-STr* and repeated exposure neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), aluminum diethylphosphinate meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if aluminum diethylphosphinate were assigned a High score for the data gap E, or a Very High score for STs or Ns, it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal, and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 3 ("Use but Search for Use but Still Opportunity for Improvements") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Aluminum Diethylphosphinate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	*L*	*L*	DG	**L**	DG	**L**	DG	**L**	**L**	*L*	**L**	**L**	**L**	**L**	*vH*	*vL*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Aluminum Diethylphosphinate (CAS #225789-38-8)

Method Version: GreenScreen® Version 1.3[1]
Assessment Type[2]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment Prepared By:
Name: Kristen Schaefer, M.F.S.

Title: Associate Toxicologist
Organization: ToxServices LLC
Date: August 15, 2010

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: August 15, 2010

GreenScreen® Assessment Updated By:
Name: Emily Golden, M.F.S.

Title: Toxicologist
Organization: ToxServices LLC
Date: March 14, 2011

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: March 14, 2011

GreenScreen® Assessment Updated By:
Name: Chris Schlosser, M.F.S.

Title: Associate Toxicologist
Organization: ToxServices LLC
Date: February 27, 2012
Updated: April 18, 2012; October 14, 2012

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: February 29, 2012
Updated: April 29, 2012; May 30, 2012; October 16, 2012

GreenScreen® Assessment Updated By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.

Title: Toxicologist
Organization: ToxServices LLC
Date: October 29, 2013

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: 10/29/2013

GreenScreen® Assessment Updated By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: January 21, 2016

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: January 21, 2016

GreenScreen® Assessment Updated By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.

Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.

[1] Use GreenScreen® Hazard Assessment Guidance (Guidance) v1.3
[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)

Title: Toxicologist
Organization: ToxServices LLC
Date: August 18, 2016

Title: Toxicologist
Organization: ToxServices LLC
Date: October 31, 2016

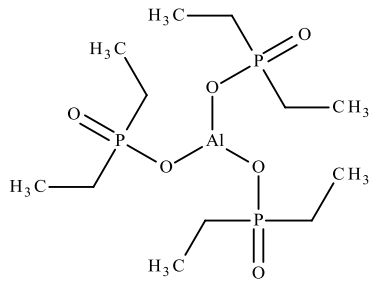
Confirm application of the *Disclosure and Assessment Rules and Best Practice*[3]: (List disclosure threshold and any deviations) No relevant information is available. The screen is performed on the theoretical pure substance.

Notes related to production specific attributes[4]:
No relevant information is available. The screen is performed on the theoretical pure substance.

Chemical Name: Aluminum diethylphosphinate

CAS Number: 225789-38-8

Chemical Structure(s):



Also called: Exolit OP 930; Exolit OP 935; Exolit OP 945; Exolit OP 1230; Exolit OP 1240; Aluminium diethylphosphinate; Aluminium tris(diethylphosphinate)

Suitable analogs or moieties of chemicals used in this assessment (CAS #'s):
An adequate toxicological dataset was available for aluminum diethylphosphinate. No suitable surrogates were identified for the endpoints with data gaps.

Identify Applications/Functional Uses:
Flame retardant for polyamides, polyesters, and thermoset resins (U.S. EPA 2014, 2015b).

GreenScreen® Summary Rating for Aluminum Diethylphosphinate[5,6 7,8]: Aluminum diethylphosphinate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvements") (CPA 2016c). This score is based on the following hazard score:

[3] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

[4] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen assessment of the generic chemical by CAS #.

[5] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[6] See Appendix A for a glossary of hazard endpoint acronyms

[7] For inorganic chemicals only, see GreenScreen Guidance v1.3 Section 13 (Exceptions for Persistence).

- Benchmark 3a
    - Very High Persistence-P

A data gap (DG) exists for endocrine activity-E. The lack of data for single exposure systemic toxicity-STs and single exposure neurotoxicity-Ns is not counted in the benchmarking process as data are available for repeated exposure systemic toxicity-STr* and repeated exposure neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), aluminum diethylphosphinate meets requirements for a GreenScreen® Benchmark Score of 3 despite the hazard data gaps. In a worst-case scenario, if aluminum diethylphosphinate were assigned a High score for the data gap E, or a Very High score for STs or Ns, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Aluminum Diethylphosphinate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	*L*	*L*	DG	**L**	DG	**L**	DG	**L**	**L**	*L*	**L**	**L**	**L**	**L**	*vH*	*vL*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e. vH, H, M, and L) instead of three (i.e. H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings[9]:
Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[10]

Aluminium diethylphosphinate decomposes before boiling at temperatures above 300ºC. Major pyrolysis products are diethylphosphinic acid, ethylphosphonic acid, phosphoric acid, and their respective salts (with aluminum) according to a confidential study reviewed by U.S. EPA (2014). As none of the environmental transformation products has an LT-1 score (Table 1), the Benchmark Score for aluminum diethylphosphinate is not modified by transformation products.

[8] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen Guidance v1.3 Section 8.2.1.
[9] See GreenScreen Guidance v1.3 Section 12.
[10] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

Table 1: Transformation Product Summary Table						
Functional Use	**Life Cycle Stage**	**Transformation Pathway**	**Transformation Products**	**CAS #**	**Feasible and Relevant?**	**GreenScreen® List Translator Score or Benchmark Score[11,12]**
Flame retardant	End of life	Pyrolysis	Aluminum	7429-90-5	Yes	LT-P1 (TEDX potential endocrine disruptor; AOEC asthmagen)
Flame retardant	End of life	Pyrolysis	Phosphate	14265-44-2	Yes	No hazards listed in Pharos
Flame retardant	End of life	Pyrolysis	Diethylphosphinic acid	813-76-3	Yes	No hazards listed in Pharos
Flame retardant	End of life	Pyrolysis	Ethylphosphonic acid	6779-09-5	Yes	Not in Pharos database
Flame retardant	End of life	Pyrolysis	Phosphoric acid	7664-38-2	Yes	LT-U

Introduction

Aluminum diethylphosphinate is an inorganic compound that is used as a flame retardant. It has high temperature stability, is insoluble in water (<1 mg/L at 20˚C) and organic solvents, and owes its efficiency to its high phosphorus content (23-24%) (U.S. EPA 2015b). Aluminum diethylphosphinate is marketed by Clariant Corp. under the tradenames Exolit OP 1230, Exolit OP 1240, Exolit OP 930, Exolit OP 935 and Exolit OP 945. These differ by particle size (5 to 40 µm) and variations in the production process. Aluminum diethylphosphinate is used on its own in engineering plastics like polyamides and polyesters or thermosets like epoxy resins. In addition, it is combined with nitrogen-containing and other synergists in special applications.

ToxServices assessed aluminum diethylphosphinate against GreenScreen® Version 1.3 (CPA 2016a) following procedures outlined in ToxServices' SOPs 1.37 and 1.69 (GreenScreen® Hazard Assessment) (ToxServices 2016a,b).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2016). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015). Aluminum diethylphosphinate is not listed on the SCP SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2016a.b). Pharos (Pharos 2016) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b)[13] and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each

[11] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2016a,b). Pharos (Pharos 2016) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[12] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen Guidance)
[13] DOT lists are not required lists for GreenScreen List Translator v1.3. They are reference lists only.

human health and environmental endpoint. The output for aluminum diethylphosphinate can be found in Appendix C.

- Aluminum diethylphosphinate is an LT-U chemical when screened using Pharos, and therefore a full GreenScreen® is required.

Hazard Statement and Occupational Control

Aluminum diethylphosphinate is not classified under GHS or associated with any H Statements on the product SDS (Clariant 2010). There are no harmonized GHS classifications in the EU. No occupational exposure limits were identified.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment of Aluminum Diethylphosphinate (CAS #225789-38-8)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respiratory: Dust mask; Hand: Antistatic gloves, PVC or PE gloves; Eye: Tightly fitting safety glasses Body: Protective clothing	Clariant 2010	None identified	Clariant 2010; ECHA 2016; ChemIDplus 2016

Physicochemical Properties of Aluminum Diethylphosphinate

Aluminum diethylphosphinate is a white, fine-grade powder under standard temperature and pressure. It is estimated to have a low vapor pressure (less than 10^{-8} mm Hg) indicating that it exists mostly in the solid phase. It dissolves very slowly in water but it predicted to be more soluble in water than in octanol (estimated log K_{ow} = -0.44). Its log K_{ow} value indicates that it is not likely to bioaccumulate in aquatic biota.

Table 3: Physical and Chemical Properties of Aluminum Diethylphosphinate (CAS #225789-38-8)

Property	Value	Reference
Molecular formula	$3[C_4H_{11}PO_2].Al$	U.S. EPA 2014
SMILES Notation	CCP(=O)(CC)O[Al](OP(=O)(CC)CC)OP(=O)(CC)CC	U.S. EPA 2014
Molecular weight	390.27	U.S. EPA 2014
Physical state	Solid	U.S. EPA 2014
Appearance	White, fine-grade powder	Clariant 2010
Melting point	Decomposes at 300ºC and above Greater than 400ºC	U.S. EPA 2014
Vapor pressure	Less than 10^{-8} mm Hg (estimated)	U.S. EPA 2014
Water solubility	$2.5x10^3$ mg/L (low wettability and very slow dissolution. This gives a kinetically controlled solubility of <1 mg/L. If the chemical is formed by precipitation of a soluble salt, the remaining equilibrium solubility of $2.5x10^3$ mg/L is found, which is assumed to be the limit of solubility under ideal conditions)	U.S. EPA 2014
Dissociation constant	Dissociated within 24 hours at pH 4.5 during MITI test	U.S. EPA 2014

Table 3: Physical and Chemical Properties of Aluminum Diethylphosphinate (CAS #225789-38-8)		
Property	**Value**	**Reference**
Density/specific gravity	1.2 g/cm^3 at 4ºC	NICNAS 2005 U.S. EPA 2015b
Partition coefficient	Log K_{ow} = -0.44 (estimated)	U.S. EPA 2014

Toxicokinetics

- Clariant 1998, U.S. EPA 2014
  - In a non-GLP *in vivo* toxicokinetic study performed according to a method similar to OECD Guideline 417, male Fischer 344 rats (2/dose) were exposed to single applications of aluminum diethylphosphinate at 180 or 1,000 mg/kg by gavage, and then kept in metabolism cages to collect urine and feces every 12 hours for up to 72 hours after exposure. 10.5% and 13.6% of the administered doses were recovered in the urine as free phosphinic acid at the low and high doses, respectively, while 48.2 and 41.1% were unabsorbed and excreted unchanged in the feces at the low and high doses, respectively. However, the total recovery from urine and feces was only 58.7 and 54.7%, respectively, at the low and high doses. The fate of the remaining fractions is unclear. No test substance was detected in either urine or feces after 36 hours. *The reliability of this study is questionable due to the low recovery of the test material. U.S. EPA noted that the number of animals tested (2/dose) was small.*
- U.S. EPA 2014
  - Based on the physicochemical properties of aluminum diethylphosphinate and confidential analogs, U.S. EPA concluded that the compound is not absorbed through skin as neat solid. However, it is expected to be well-absorbed through lungs and gastrointestinal tract.
- Clariant 2016a
  - The bioaccessibility of aluminum and phosphorus from aluminum diethylphosphinate was examined *in vitro* in the patented TNO Gastro-Intestinal Model (TIM). TIM is composed of a series of compartments interconnected by valves regulating gastrointestinal transit to represent the GI tract from stomach to small intestine. The temperature, speed of fluid movement, acidity, electrolyte concentrations, swallowed saliva, "secretion" of gastric acid and enzymes, pancreatic juice with enzymes, and bile salts are specifically controlled in different compartments. The whole system is regulated by a computer. This model has been validated by comparison with *in vivo* studies (TNO 2013). In this experiment, the TIM model for humans under fasting state was used as a worst case scenario. The model was run with and without 9 g of aluminum diethylphosphinate. Hourly fractions were collected from the dialysate of the jejunum and ileum simulation compartments, which represent bioaccessible fraction, and from the ileum efflux, which represents non-bioaccessible fraction. Samples were analyzed for aluminum and phosphorus content. The study results indicate that 0.1% of the administered aluminum and 26.3% of phosphorus were bioaccessible, and the study authors concluded that aluminum from aluminum diethylphosphinate is not bioaccessible or bioaccumulating.
- Hendriks et al. 2015
  - A non-guideline, peer-reviewed *in vivo* study was conducted to examine the developmental neurotoxicity of three halogen-free flame retardants, including aluminum diethylphosphinate. Male C57Bl/6 pups (6-9/dose) received a single oral dose of aluminum diethylphosphinate (99% pure) via gavage at 0 or 82.4 mg/kg on postnatal day 10, which is the peak date of brain growth spurt. They were sacrificed between postnatal days 17 and 19, which is the period just after the peak of the brain growth spurt. Developmental

neurotoxicity endpoints examined are described in the Developmental Toxicity section below. The internal dose of aluminum diethylphosphinate was analyzed in the liver, muscle, and non-cortex brain tissues. Aluminum was not detectable in brain, muscle and liver, indicating low bioavailability and/or rapid elimination/metabolism.

- Hendriks and Westerink 2015
    - The hydrophilicity of aluminum diethylphosphinate (log K_{ow} of -0.44) limits the absorption of the compound in the gastrointestinal tract, through the blood-brain barrier, and through the placental barrier. Therefore, the bioavailability of aluminum diethylphosphinate is likely to be very low. It should be noted that a metal-based phosphorous flame retardant may dissociate under some conditions, even though levels of aluminum are unlikely to reach high levels sufficient to be a health concern.
- In summary, U.S. EPA (2014) estimated that aluminum diethylphosphinate is bioavailable through inhalation and oral routes of exposure based on physicochemical properties and confidential analog data, as well as the *in vivo* toxicokinetic study. This *in vivo* study indicates that the phosphorus in the compound is bioavailable (~10% excreted as phosphinic acid in the urine), but the bioavailability of aluminum was not addressed. In addition, the low total recovery of only 50% threw doubts on the reliability of these results. Clariant performed an *in vitro* bioaccessibility study using the TIM model, which is claimed to have been validated by comparison with *in vivo* data (no details regarding validation procedures were provided), to examine the bioaccessibility of aluminum diethylphosphinate through the GI tract. The results indicate that aluminum from aluminum diethylphosphinate is not bioaccessible (0.1%), while a limited amount of phosphorus is bioaccessible (26.3%). The identities of metabolites were not analyzed. These results were further supported by the *in vivo* mice study conducted by Hendriks et al. (2015), which did not find statistically significant differences in aluminum levels in the liver, brain and muscle after pups were exposed to a single oral dose of aluminum diethylphosphinate. In addition, the lack of neurotoxicity in the 28-day oral toxicity study in rats (discussed below) supports low bioavailability of the aluminum, which is a known neurotoxicant. The *in vitro* study and the *in vivo* study were not evaluated in EPA's 2014 report. The total weight of evidence indicates that aluminum diethylphosphinate is rapidly excreted from the body after oral ingestion. Data suggest that aluminum from diethylphosphinate is not bioavailable while phosphinate has some bioavailability. No information is available for the inhalation route of exposure. However, based on its low wettability and very slow dissolution in water (Table 3), as well as lack of bioavailability in the *in vitro* assay even under acidic conditions in the stomach simulation compartment, the aluminum moiety is unlikely to be significantly bioavailable through inhalation, while the bioavailability of phosphorous through this route cannot be ruled out. Finally, dermal absorption of aluminum diethylphosphinate is expected to be negligible based on U.S. EPA's expert opinion.

Hazard Classification Summary Section:

<u>Group I Human Health Effects (Group I Human)</u>

Carcinogenicity (C) Score (H, M, or L): *L*

Aluminum diethylphosphinate was assigned a score of Low for carcinogenicity based on the U.S. EPA expert opinion and modeling that indicate it is not likely to be carcinogenic. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when negative data, no structural alerts, and no GHS classification are available (CPA 2016ba). The confidence in the score is low as it is not based on authoritative lists or measured data.

- Authoritative and Screening Lists

  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2014
  - Not expected to be carcinogenic based on expert judgment on data on confidential metal salts analogs.
- U.S. EPA 2013
  - OncoLogic (v8.0) predicts that the aluminum carbohydrate complexes have low to moderate carcinogenic potential (see Appendix D).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for mutagenicity/genotoxicity based on the negative results for mutagenicity and clastogenicity obtained in a pair of *in vitro* studies and an *in vivo* study. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data for mutagenicity and clastogenicity, no structural alerts, and no GHS classification are available (CPA 2016b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - *In vitro*: Negative results for mutagenicity were obtained in an Ames test. Exolit OP 930/1230 did not cause any reverse mutations in *Salmonella typhimurium* test strains TA 98, TA 100, TA1535, and TA1537 exposed to concentrations ranging from 4 to 5,000 µg/plate, with and without a metabolic activation.
  - *In vitro:* Negative results for clastogenicity were obtained in a chromosomal aberration test. Exolit OP 930/1230 was not clastogenic to Chinese Hamster V79 cells in a chromosomal aberration test at concentrations ranging from 1.0 to 700 µg/mL in the presence of metabolic activation.
- U.S. EPA 2014
  - *In vivo*: Negative results for clastogenicity were obtained in a mammalian erythrocyte micronucleus test conducted according to OECD 474. NMRI mice were administered the test compound orally. No further details were provided.

Reproductive Toxicity (R) Score (H, M, or L): *L*
Aluminum diethylphosphinate was assigned a score of Low for reproductive toxicity based on the lack of reproductive toxicity observed in an OECD 421 reproductive/developmental toxicity screening test in rats. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a). The confidence in the score is reduced as only a screening study is available.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2014, 2015b
  - A reproductive/developmental toxicity screening test conducted according to OECD 421 was performed with Sprague-Dawley rats (number per sex not specified) administered oral doses (specific oral route not specified) of 0, 250, or 1,000 mg/kg/day for 15 days prior to mating and through gestation and lactation up to postnatal day 3. The animals were evaluated for clinical signs of toxicity, body weight and body weight gain, food consumption, sperm parameters (motility, morphology, and concentration), estrous cyclicity,

gestation length, number of implantation and corpora lutea, and sex ratios. Reduced terminal body weight and absolute and relative kidney weights were observed in high dose males. An increase in the number of days of pre-coital interval and a reduction in the number of copulation plugs was observed in the high dose group (both effects described as minor). No other treatment-related effects were observed and a reproductive NOAEL of 1,000 mg/kg/day was identified.
    - Aluminum diethylphosphinate is estimated to be of low hazard for reproductive effects resulting from the presence of a bioavailable metal species, by professional judgment based on a comparison to analogous metal salts.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Aluminum diethylphosphinate was assigned a score of Low for developmental toxicity based on lack of effects in guideline reproductive and developmental toxicity studies, and in *in vitro* and *in vivo* studies specifically examining general and developmental neurotoxicity. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2016b). The confidence in the score was reduced as limited neurotoxicity endpoints were examined in the available studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2014, 2015b
    - A reproductive/developmental toxicity screening test conducted according to OECD Guideline 421 was performed with Sprague-Dawley rats (number per sex not specified) administered oral doses (specific oral route not specified) of 0, 250, or 1,000 mg/kg/day for 15 days prior to mating and through gestation and lactation up to postnatal day 3. The animals were evaluated for clinical signs of toxicity, body weight and body weight gain, food consumption, gestation length, number of implantation and corpora lutea, sex ratios, and macroscopic anomalies of pups. No treatment-related effects were observed on the incidence of macroscopic anomalies observed in pups dying or sacrificed at the end of the study. No other treatment-related effects were observed and a developmental NOAEL of 1,000 mg/kg/day was identified.
    - Aluminum diethylphosphinate is expected to have a moderate hazard for developmental toxicity given exposure may result in neurodevelopmental effects based on the presence of a phosphinate; there were no experimental studies specifically designed to evaluate the neurodevelopmental endpoint located. The potential for neurodevelopmental effects cannot be ruled out.
- Clariant 2016a, BSL BIOSERVICE 2013
    - A developmental toxicity study was conducted under GLP according to OECD Guideline 414. Pregnant Wistar rats (24-25/dose) were exposed to aluminum diethylphosphinate (Tradename Exolit OP 1230, purity 96.9%) by oral gavage on gestation days 5 to 19 at 0, 100, 300 or 1,000 mg/kg/day. Polyethyleneglycol 400 was used as the vehicle. Maternal animals were examined for clinical signs, body weight, food consumption, gross necropsy, uterus and ovary weight, number of implantations, resorptions, litter size, and live and dead fetuses. Fetuses were examined for sex, weight, external abnormalities, visceral and craniofacial abnormalities, and skeletal abnormalities. The high dose animals had slight diarrhea and the mid and high dose animals showed symptoms of discomfort such as moving the bedding and piloerection. Treatment groups had a slight increase in food consumption, but there was no dose-response. Few gross external abnormalities were observed in both

control and treatment groups, with no statistically significant differences, and were therefore determined to be incidental. Treated groups had increased skeletal abnormalities, but the authors concluded that they were either not treatment-related or of no toxicological significance. Visceral abnormalities were found in both control and treated groups and were concluded to be not treatment-related and of no toxicological significance. Craniofacial examination identified visceral abnormalities in both control and treatment groups, most of which are not statistically significant. The authors determined that none of these findings were biologically relevant. The study authors identified a NOAEL of 1,000 mg/kg/day for maternal toxicity based on lack of changes in body weight development despite clinical symptoms. The study authors identified a NOAEL of 1,000 mg/kg/day for developmental toxicity based on lack of effects identified at the highest dose tested.

- Hendriks et al. 2014
    - A peer-reviewed *in vitro* cytotoxicity and neurotoxicity study on brominated and halogen-free flame retardants, including aluminum diethylphosphinate, was conducted in rat dopaminergic pheochromocytoma (PC12) and rat neuroblastoma (B35) cells. Parameters examined include cytotoxicity, production of reactive oxygen species and calcium homeostasis. Among the thirteen flame retardants studied, aluminum diethylphosphinate was one of the three chemicals with negligible neurotoxicity potency, which is the lowest toxicity rank. The study authors recommended aluminum diethylphosphinate as one of the best candidate alternatives for brominated flame retardants, and called for further *in vitro* and *in vivo* study to confirm the findings.
- Hendriks et al. 2015
    - A non-guideline, peer-reviewed *in vivo* study was conducted to examine the developmental neurotoxicity of three halogen-free flame retardants, including aluminum diethylphosphinate. Male C57Bl/6 pups (6-9/dose) received a single oral dose of aluminum diethylphosphinate (99% pure) via gavage at 0 or 82.4 mg/kg on postnatal day 10, which is the peak date of brain growth spurt. They were sacrificed between postnatal days 17 and 19, which is the period just after the peak of the brain growth spurt. Synaptic transmission and activity-dependent plasticity in the hippocampal CA1 region was investigated in hippocampal slices. Protein expression in the cortex was examined for CaMK-II, GAP-43, GluR1, PSD95 and synaptophysin. In addition, the internal dose of aluminum diethylphosphinate was analyzed in the liver, muscle, and non-cortex brain tissues. Aluminum diethylphosphinate-treated pups had normal body weight development and did not show signs of general toxicity. The treatment did not affect basal excitability and synaptic transmission in the brain, but slightly (not statistically significantly) increased the long-term potentiation. Protein expression of neurotransmitter receptors and protein kinases critical for induction and maintenance of long term potentiation was not affected by the treatment. In addition, aluminum was not detectable in brain, muscle and liver, indicating low bioavailability and/or rapid elimination/metabolism. The study authors concluded that single neonatal exposure on postnatal day 10 to aluminum diethylphosphinate only slightly and insignificantly affected neurodevelopment and synaptic plasticity in mice. The authors suggested that aluminum diethylphosphinate as a potentially suitable alternative flame retardant for brominated flame retardants.
- Based on the weight of evidence, a score of Low was assigned. Guideline reproductive and developmental toxicity studies revealed that aluminum diethylphosphinate is not likely to be a developmental toxicant. While U.S. EPA determined that the compound has a potential to be a developmental neurotoxicant based on the presence of bioavailable phosphinate moiety, and the lack of data specifically examining developmental neurotoxicity endpoints. Additional *in vitro* and *in*

vivo data became available after U.S. EPA's evaluation, and suggest that aluminum diethylphosphinate is not a developmental neurotoxicant. However, uncertainties exist as only limited neurotoxicity endpoints were examined in the studies identified. Therefore, the score of Low was assigned with low confidence.

Endocrine Activity (E) Score (H, M, or L): DG
Aluminum diethylphosphinate was assigned a score of Data Gap for endocrine activity based on lack of sufficient data. Although no effects were observed in reproductive and repeated dose toxicity studies on several endocrine-related organs, no studies were specifically designed to rule out endocrine activity in all endocrine pathways.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Clariant 2016a
  - While no studies were conducted specifically to test the endocrine activity of aluminum diethylphosphinate, no effects (weight and histopathology) were observed on the thyroid, ovaries, testes, epididymides, adrenal glands, prostate, uterus, and seminal vesicles (weight only) in the previously described reproductive/developmental screening test conducted according to OECD Guideline 421, and in the 28-day oral toxicity study performed according to OECD Guideline 407 as described under repeated dose systemic toxicity section below. In addition, exposure to the compound did not affect estrus cycle or sperm parameters in the OECD 421 study. *In silico* prediction using Derek Nexus Program v 4.0.5 was negative for estrogenicity.

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values greater than 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2016b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - *Oral:* LD_{50} (rat) = greater than 2,000 mg/kg
  - *Dermal:* LD_{50} (rat) = greater than 2,000 mg/kg

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L):** DG
Aluminum diethylphosphinate was assigned a score of Data Gap for systemic toxicity (single dose) based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

***Group II* Score (repeated dose)* (H, M, or L): L**
Aluminum diethylphosphinate was assigned a score of Low for systemic toxicity (repeated dose) based on lack of toxicities observed in a 28-day oral study at doses up to 1,000 mg/kg/day, and lack of bioavailability for aluminum. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2016b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - In a 28-day oral gavage study (OECD TG 407) in Wistar rats (5/sex) given 0, 62.5, 250, or 1,000 mg/kg/day in drinking water, aluminum diethylphosphinate did not induce any adverse effects including neuro- or organ-toxicity. High dose males exhibited macerated feces on day 24. In addition, high dose males showed increased relative liver weights. High dose females exhibited decreased mean cell volume and an increase in leukocyte count but other red blood cell parameters were normal. All clinical and hematological observations and changes in organ weights remained within the normal physiological range. The NOAEL was established as 1,000 mg/kg/day. *This NOAEL value is above the duration-adjusted (i.e. tripled from 90-day to 28-day studies) guidance value of 300 mg/kg/day for GHS classification.*
- U.S. EPA 2015b
  - Aluminum diethylphosphinate is estimated to be of moderate hazard for immunotoxicity, due to the presence of a bioavailable metal species (Aluminum) and based on comparison to analogous metal salts and professional judgement.
- Based on the weight of evidence, a score of Low was assigned. U.S. EPA's moderate concern on the immunotoxicity was based on the presumed bioavailability of aluminum from aluminum diethylphosphinate. However, as discussed in the Toxicokinetics section, the weight of evidence considering new data that became available after U.S. EPA's evaluation support that aluminum is unlikely to be bioavailable *in vivo*.

Neurotoxicity (N)
***Group II Score (single dose)* (vH, H, M, or L):** DG
Aluminum diethylphosphinate was assigned a score of Data Gap for neurotoxicity (single dose) based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).

- No data were identified for this endpoint.

Group II* Score (repeated dose) **(H, M, or L): L**
Aluminum diethylphosphinate was assigned a score of Low for neurotoxicity (repeated dose) based on lack neurotoxicity in a 28-day repeated-dose toxicity study and expected lack of bioavailability for aluminum from aluminum diethylphosphinate. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2016b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- NICNAS 2005, Clariant 2016a
  - In the 28-day repeated dose oral gavage study conducted according to OECD 407 in rats as described above in the repeated dose toxicity study section, neurotoxicity parameters examined included daily behavior observation, weekly open field observation, sensory function, motor activity, rearings, forelimb and hind limb grip strength, and landing foot-spread. No changes were observed on these parameters. Therefore, the NOAEL for neurotoxicity was 1,000 mg/kg/day, the highest dose tested.
- U.S. EPA 2014
  - Aluminum diethylphosphinate is expected to have a moderate hazard potential for neurotoxicity as the results of bioavailable (inhalation and oral, but not dermal) aluminum in the compound.
- Hendriks and Westerink 2015
  - Based on the expected low bioavailability and the low neurotoxicity observed in two neurotoxicity studies performed *in vitro* and *ex vivo* (Hendriks et al. 2014, 2015), aluminum diethylphosphinate demonstrated a low neurotoxic potential. Although additional data regarding endpoints such as human exposure levels, break-down products, possible metabolites, and persistence in the environment are lacking, the authors suggested that aluminum diethylphosphinate is a suitable alternative flame retardant for brominated flame retardants.
- Based on the weight of evidence, a score of Low was assigned. U.S. EPA concluded that aluminum diethylphosphinate has a moderate concern for neurotoxicity, but the 28-day repeated dose toxicity study with neurotoxicity examination was not included for consideration for this endpoint by the agency, and the conclusion was made based on estimated bioavailability of aluminum. As discussed in the Toxicokinetics section above, the weight of evidence suggests that the aluminum in the compound is unlikely to be bioavailable *in vivo*. In addition, the 28-day study did not find any neurotoxicity up to the highest dose tested (i.e. 1,000 mg/kg/day). Therefore, GHS classification on neurotoxicity is not warranted.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for skin sensitization based on the lack of dermal sensitization reactions observed in a guinea pig maximization test. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data, no structural alerts, and no GHS classification are available (CPA 2016b). The confidence in the score is high as it is based on a high quality study.

- Authoritative and Screening Lists

  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005:
  - No dermal reactions were seen in guinea pigs indicative of skin sensitization following an OECD 406 skin sensitization (guinea pig maximization) Test. The test animals (10/group, 5/control) were administered the test substance either intra-dermally (5% w/v in sesame oil) or topically (25% w/v in sesame oil) using Freund's complete adjuvant as an immune enhancer. Intradermal administration resulted in slight erythema and edema. Animals administered the test substance dermally exhibited severe erythema and edema, indurated, scabbed and encrusted skin as well as necrosis at the sites previously treated with Freund's Complete Adjuvant. Administration of the test substance or vehicle alone produced no signs of irritation.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): *L*

Aluminum diethylphosphinate was assigned a score of Low for respiratory sensitization based on lack of dermal sensitization potential and the lack of structural alerts for respiratory sensitization, according to the evaluation strategy proposed by ECHA. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2016b). The confidence in the score was reduced as the ECHA strategy is still in draft version, and that no experimental data were available specific for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.
- ECHA 2015
  - The respiratory sensitization potential of aluminum diethylphosphinate was evaluated using the strategy proposed by ECHA (Figure R.7.3-3 of ECHA 2015). As aluminum diethylphosphinate was negative in a guinea pig maximization assay as described in the Skin Sensitization section above and lacks structural alerts for respiratory sensitization (OECD 2016), it is unlikely to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L

Aluminum diethylphosphinate was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation observed in a rabbit study. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a). The confidence in the score is high as it is based on a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - In an OECD TG 404 Acute Dermal Irritation/Corrosion study in New Zealand albino rabbits (3/vehicle used), the test substance mixed with either polyethylene glycol or deionized water as test vehicles produced no signs of irritation following 72 hours of exposure. The dose and/or concentration of the test substance were not provided.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for eye irritation/corrosivity based on lack of significant effects observed in multiple studies. The transient and slight irritation observed was attributed to mechanical effects. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2016b). The confidence in the score is high as it is based on well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - Two OECD TG 405 Acute Eye Irritation/Corrosion tests were performed on New Zealand albino rabbits (3/study). After 72 hours of administration, animals exhibited swelling, increased redness of injected blood vessels, reddened iris, opaque corneas, and colorless discharge from the eye. All symptoms cleared within 3 days after administration. The test substance was concluded to be slightly irritating. The dose of the test substance was not provided. No further details were provided.
- U.S EPA 2014
  - In a confidential study submitted to EPA, the compound tested to be non-irritating to the eye of rabbits. No further details were provided.
- Clariant 2016a (this may be one of the two studies described by NICNAS above)
  - In an ocular irritation study performed according to OECD Guideline 405, three New Zealand White rabbits were exposed to 0.1 g aluminum diethylphosphinate in the conjunctival sac of the left eye. The right eye served as the control. The treated eyes were washed 24 hours afterwards. The eyes were examined 1, 24, 48 and 72 hours after exposure. Definitely injected blood vessels up to diffuse, crimson red color and slight swelling were observed at 1 hour post exposure. In addition, white mucous eye discharge was noted a few hours after application. One animal had definitely injected blood vessels at conjunctiva at 24 hours. All signs of irritation disappeared by 48 hours. The study authors concluded that the test compound is not classifiable as an ocular irritant, and the observed irritation effects were due to mechanic rubbing of solids.

<u>Ecotoxicity (Ecotox)</u>

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values of greater than 100 mg/L for all three trophic levels. The inhibition of algal growth observed in the GLP-compliant algae study was attributed to the test compound's impact on pH. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 100 mg/L (CPA 2016b). The confidence in the score is high as it was based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005, Schneider-Reigl 2016
  - 96-hour LC_{50} (*Danio rerio*, zebrafish) = greater than 100 mg/L (nominal) (EU Method C.1) (test substance: commercial preparation containing 83.3% a.i.)

  - 48-hour LC_{50} (*Daphnia magna*) greater than 100 mg/L (nominal) (OECD 202) (test substance: commercial preparation containing 83.3% a.i.)
- U.S. EPA 2014, Schneider-Reigl 2016
  - 96-hour LC_{50} (*D. rerio*) = greater than 9.2 to greater than 11 mg/L
  - 48-hour LC_{50} (*D. magna*) = greater than 33 to greater than 33.7 mg/L (test substance: commercial preparation containing 83.3% a.i.)
  - 72-hour E_bC_{50} (*Scenedesmus subspicatus*, green algae) = 60 mg/L, E_rC_{50} = 76 mg/L. (test substance: commercial preparation containing 83.3% a.i.)
  - 72-hour EC_{50} (green algae unspecified species) = 50 mg/L
  - 72-hour EC_{50} (*S. subspicatus*, green algae) = greater than 180 mg/L (EU Method C.3)
- Beard 2016, Clariant 2016b
  - Clariant clarified that the all the data described above were provided by Clariant. In the 72-hour study in green algae (GLP compliant, OECD Guideline 201), a 72h E_bC_{50} of 60 mg/L for biomass, and a 72h E_rC_{50} of 76 mg/L for growth rate were identified in the same study using a preparation of aluminum diethylphosphinate that is 83% pure. U.S. EPA (2014) calculated the E_bC_{50} of 50 mg/L for the active substance by multiplying 60 mg/L by 0.83. However, the observed toxicity was attributed to reduced pH of the test media due to the addition of the test substance, rather than the specific toxicity of aluminum diethylphosphinate. The pH of the test medium at nominal concentrations of 3.2, 5.7, 10, 18, 32, 58, 100 and 180 mg/L were 7.83, 7.74, 7.65, 7.47, 7.31, 7.02, 5.92 and 4.44, respectively. Therefore, another group was included with a nominal concentration of 180 mg/L and pH adjusted to 7.98 (pH of negative control was 7.92). No growth inhibition was observed, and the EC_{50} as well as NOEC were determined to be > 180 mg/L for this study. It was argued that the natural water has buffering capacity and therefore release of aluminum diethylphosphinate is unlikely to overwhelm the buffering capacity of natural waters. Therefore, the EC_{50} of > 180 mg/L is most relevant for the assessment of this endpoint among all values for algae.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L

Aluminum diethylphosphinate was assigned a score of Low for chronic aquatic toxicity based on EC_{10} values for the pure substance in chronic studies in fish, daphnia and algae. The OECD notes that recent developments have led to recommendation of regression-based point estimates rather than NOEC values as estimates of toxicity, EFSA recommends the use of EC_{10} instead of NOEC for risk assessment, and the ECOSAR program predicts chronic values (ChVs), which are the geometric means of the NOECs and LOECs. The ChVs are routinely used by various regulatory bodies as the basis for classification. Therefore, while the lowest NOEC is 10 mg/L in the chronic study in daphnia, which is right on the border of GreenScreen® guidance values for a Low and a Moderate, the weight of evidence suggests that adverse effects are unlikely to occur at 10 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2016b). The confidence in the score is high as it is based on high quality data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005, Schneider-Reigl 2016
  - 21-day LC_{50} (*D. magna*) = 22.3 mg/L (test substance: commercial preparation containing 100% a.i.)
  - 21-day NOEC (*D. magna*) = 10 mg/L (test substance: commercial preparation containing 100% a.i.)

- U.S. EPA 2014, Schneider-Reigl 2016
    - 28-day NOEC (*D. rerio*) (nominal) = 100 mg/L (OECD 215) (test substance: commercial preparation containing 98.7% a.i.)
    - ChV (fish) = 48 mg/L (estimated) (no further details were provided)
    - 21-day NOEC (*D. magna*) = 10 mg/L and LOEC = 32 mg/L for immobility and reproduction (test substance: commercial preparation containing 100% a.i.)
    - ChV (green algae) = 1.8 mg/L (measured, confidential study)
- Beard 2016, Clariant 2016b
    - Clariant clarified that the all the data described above were provided by Clariant. For the GLP-compliant (OECD Guideline 211) 21-day study in daphnia that reported a NOEC of 10 mg/L and LOEC of 32 mg/L, an EC_{10} of 12.8 mg/L for reproduction and an EC_{10} of 11.2 mg/L for mortality were derived. This study was performed on the 100% aluminum diethylphosphinate.
    - The chronic value of 1.8 mg/L for algae was derived from the NOEL of 2.2 mg/L for both biomass and growth inhibition in the 72-hour algae study. The NOEL was multiplied by the purity of the test substance (83%) to obtain the value of 1.8 mg/L for the pure substance. The E_bC_{10} of this study is 29 mg/L and the E_rC_{10} is 34 mg/L (equivalent to values of 24 and 28 mg/L, respectively, for the pure substance obtained by multiplying 0.83).
        - As the observed inhibition of algal growth is most likely attributed to a pH effect, as discussed above, the NOEL of this study is considered to be 180 mg/L (equivalent to 149 mg/L active ingredient at the concentration of 83%), since no growth inhibition was observed at this concentration when the pH of the test medium was adjusted to a similar level as the control group (summarized above under Acute Aquatic Toxicity).
    - In the OECD Guideline 201 study, OECD notes that recent scientific developments have led to a recommendation of replacing the concept of NOEC with regression-based point estimates EC_x. Although a value for x has not been established for the test, a range of 10% to 20% appears to be appropriate (OECD 2011).
    - EFSA recommended EC_{10} values rather than NOECs to be used for ecotoxicity risk assessment with a protection level comparable to the level with the use of NOECs. NOEC values strongly depend on the study design, while EC_{10} is calculated based on the dose response curve (EFSA 2015).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*

Aluminum diethylphosphinate was assigned a score of Very High for persistence based on the aluminium moiety being inorganic and recalcitrant and on the nature of its flame retardant function. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when they are recalcitrant (CPA 2016b). The confidence in the score is low as it is based on expert judgement.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
    - Aluminum diethylphosphinate is not readily biodegradable
- U.S. EPA 2014
    - The organic counter-ion was estimated to have a biodegradation half-life of days-weeks (primary survey model) and weeks (ultimate survey model) using EPI Suite modeling.
    - The metal ion is estimated to be recalcitrant based on professional judgment.

- Aluminum diethylphosphinate was tested to be not inherently biodegradable in an OECD 302 C test and not readily biodegradable in an OECD 301 F test.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*
Aluminum diethylphosphinate was assigned a score of Very Low for bioaccumulation based on a BCF estimated to be less than 100. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are no greater than 100 (CPA 2016b). The confidence in the score is low as it is not based on authoritative lists or measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- NICNAS 2005
  - Aluminum diethylphosphinate rapidly dissociates in water and will not bioaccumulate.
- U.S. EPA 2014
  - Log K_{ow} = -0.44 (estimated)
  - The BCF in fish is estimated to be less than 100 by expert judgement.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Aluminum diethylphosphinate was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2012a). The confidence in the score is low as it is not based on authoritative lists or measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2014
  - Not expected to form explosive mixtures with air based on expert judgment.
- Based on the expert opinion expressed above, ToxServices did not classify aluminum diethylphosphinate as a reactive chemical under GHS criteria (UN 2015).

Flammability (F) Score (vH, H, M, or L): L
Aluminum diethylphosphinate was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2016b). The confidence in the score is high as it is based on at least one high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- U.S. EPA 2014
  - Not readily combustible measured according to guideline 96/69/EEC test A. 10.
  - No self-ignition below 402ºC (measured).
- Based on the results of the above studies, ToxServices did not classify aluminum diethylphosphinate as a flammable chemical under GHS criteria (UN 2015).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Aluminum Diethylphosphinate (CAS #225789-38-8)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Aluminum Diethylphosphinate	225789-38-8	*L*	L	*L*	*L*	DG	L	DG	L	DG	L	L	*L*	L	L	L	L	*vH*	*vL*	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	Yes	No	No	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Aluminum Diethylphosphinate	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Aluminum Diethylphosphinate	3

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

APPENDIX C: Pharos Output for Aluminum Diethylphosphinate (CAS #225789-38-8)

[225789-38-8] Aluminum diethylphosphinate

General Information | Hazards | Compound Groups | Process Chemistry Research | GreenScreen

Direct Hazards:

None identified

Potential Residual Hazards:

See Process Chemistry Research tab for details on residuals and other substances used in manufacture.

None identified

APPENDIX D: OncoLogic Carcinogenicity Results for Aluminum Diethylphosphinate (CAS #225789-38-8)

OncoLogic Justification Report For Aluminum Compounds

SUMMARY	:	
Filename	:	225789388
Substance ID	:	
Al Metal	:	MARGINAL (by inhalation/injection) LOW (by other routes)
Al Compounds	:	LOW MODERATE (for Al-carbohydrate complex by injection) LOW/MARGINAL (all other situations)

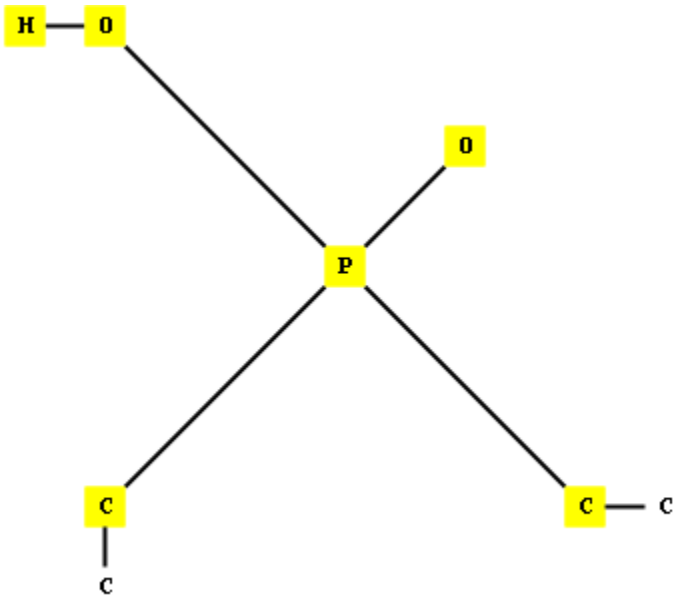
The level of concern for this substance should be based on the appropriate characteristics of the substance (e.g., form of the substance, route of exposure) and the level of concern provided by the metal.

An organic moiety is expected to be released from this substance; therefore, the organic moiety should also be evaluated for its carcinogenicity concern in the appropriate component of the Organic Subsystem.

JUSTIFICATION

Al Metal: Human exposure to Al metal powder has been associated with fibrosis of the lung (aluminosis). Subcutaneous implantation of Al foil in rodents has been shown to induce local sarcomas. Al Compounds: There is some suggestive epidemiologic evidence indicating an increased risk for cancer of the bladder and pancreas, and leukemia in workers engaged in Al production. However, these workers were also simultaneously exposed to tar oils released during the electrochemical production process. Animal data indicate that injection of Al-dextran complex can lead to induction of local tumors. No carcinogenic effects were observed after injection of several inorganic Al compounds or dextran alone. The carcinogenicity of Al-nitriloacetate complex has also been tested by i.p. injection to rats; although reported to be negative, the results should be considered inconclusive due to short duration of the study (only one year).

OncoLogic Justification Report for Alkyl phosphinate Type Compounds



SUMMARY :

CODE NUMBER : 225789388a

SUBSTANCE ID :

The concern based on structure-activity relationship consideration for this alkyl phosphinate-type compound is LOW

The concern based on the functional properties of this alkyl phosphinate-type compound is LOW

The final level of concern for this alkyl phosphinate-type compound is LOW

JUSTIFICATION:

Organophosphorus (OP) compounds are organic compounds containing phosphorus (P) as a constituent.The principal carcinogenic OP compounds are:

i) alkyl phosphates, phosphonates, phosphoroamidates and their thio derivatives (phosphorothioates,phosphorothiolates, thiophosphonates, thiophosphoroamidates.
ii) phosphoramides, and
iii) phosphorus-containing nitrogen mustards

The structural features that may affect carcinogenicity of alkyl phosphates, phosphonates, phophoroamidates, and their related thio derivates include:

i) nature of alkyl groups (size, degree of branching, halogenation) which may serve as an alkylating moiety.

ii) presence or absence of electron-withdrawing group which may enhance alkylating activity.

iii) ease or resistance to detoxifying hydrolysis which may abolish alkylating activity.

iv) potentially carcinogenic hydrolysis product(s).

Phosphoramides and certain phosphorus-containing nitrogen-mustards (e.g. cylcophosphamides) may require metabolic activation to alkylating intermediates.

The baseline level of concern for this unsubstituted alkyl phosphinate-type compound, where R1 is hydrogen, R2 is ethyl, R3 is ethyl, is LOW.

There are no published carcinogenicity data on this compound. The carcinogenicity concern for this compound is low based on structure-activity relationship analysis.

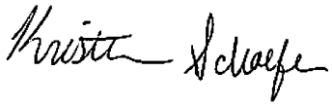
Because the structure of this compound is not suggestive of either alkylating activity or chelating properties, and it is not expected to cause liver peroxisomal proliferation, kidney or bladder stones, and the compound has tested negative for IN VITRO genotoxicity, the level of carcinogenicity concern for this compound based on these functional properties is LOW.

Considering both the structure-activity relationship (SAR) and the functional properties, the concern for carcinogenesis is the same.

The final level of concern for this alkyl phosphinate-type compound is LOW.

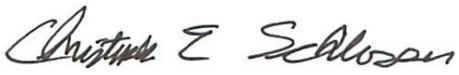
Licensed GreenScreen® Profilers

Aluminum Diethylphosphinate GreenScreen® Evaluation Prepared/ QC'd by:



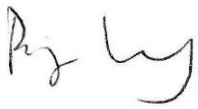
Kristen Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC

Emily Golden, M.F.S.
Toxicologist
ToxServices LLC



Christopher E. Schlosser, M.F.S.
Associate Toxicologist
ToxServices LLC

Zach Guerrette, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC



Bingxuan, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC