

Provisional Peer-Reviewed Toxicity Values for Aluminum Phosphate Salts (multiple CASRNs)



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Aluminum Phosphate Salts
(multiple CASRN_s)

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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at <https://ecomments.epa.gov/pprtv>.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α 2u-g	alpha 2u-globulin	IVF	in vitro fertilization
ACGIH	American Conference of Governmental Industrial Hygienists	LC ₅₀	median lethal concentration
AIC	Akaike's information criterion	LD ₅₀	median lethal dose
ALD	approximate lethal dosage	LOAEL	lowest-observed-adverse-effect level
ALT	alanine aminotransferase	MN	micronuclei
AR	androgen receptor	MNPCE	micronucleated polychromatic erythrocyte
AST	aspartate aminotransferase	MOA	mode of action
atm	atmosphere	MTD	maximum tolerated dose
ATSDR	Agency for Toxic Substances and Disease Registry	NAG	N-acetyl- β -D-glucosaminidase
BMC	benchmark concentration	NCI	National Cancer Institute
BMCL	benchmark concentration lower confidence limit	NOAEL	no-observed-adverse-effect level
BMD	benchmark dose	NTP	National Toxicology Program
BMDL	benchmark dose lower confidence limit	NZW	New Zealand White (rabbit breed)
BMDS	Benchmark Dose Software	OCT	ornithine carbamoyl transferase
BMR	benchmark response	ORD	Office of Research and Development
BUN	blood urea nitrogen	PBPK	physiologically based pharmacokinetic
BW	body weight	PCNA	proliferating cell nuclear antigen
CA	chromosomal aberration	PND	postnatal day
CAS	Chemical Abstracts Service	POD	point of departure
CASRN	Chemical Abstracts Service registry number	PODADJ	duration-adjusted POD
CBI	covalent binding index	QSAR	quantitative structure-activity relationship
CHO	Chinese hamster ovary (cell line cells)	RBC	red blood cell
CL	confidence limit	RDS	replicative DNA synthesis
CNS	central nervous system	RfC	inhalation reference concentration
CPHEA	Center for Public Health and Environmental Assessment	RfD	oral reference dose
CPN	chronic progressive nephropathy	RGDR	regional gas dose ratio
CYP450	cytochrome P450	RNA	ribonucleic acid
DAF	dosimetric adjustment factor	SAR	structure-activity relationship
DEN	diethylnitrosamine	SCE	sister chromatid exchange
DMSO	dimethylsulfoxide	SD	standard deviation
DNA	deoxyribonucleic acid	SDH	sorbitol dehydrogenase
EPA	Environmental Protection Agency	SE	standard error
ER	estrogen receptor	SGOT	serum glutamic oxaloacetic transaminase, also known as AST
FDA	Food and Drug Administration	SGPT	serum glutamic pyruvic transaminase, also known as ALT
FEV ₁	forced expiratory volume of 1 second	SSD	systemic scleroderma
GD	gestation day	TCA	trichloroacetic acid
GDH	glutamate dehydrogenase	TCE	trichloroethylene
GGT	γ -glutamyl transferase	TWA	time-weighted average
GSH	glutathione	UF	uncertainty factor
GST	glutathione-S-transferase	UF _A	interspecies uncertainty factor
Hb/g-A	animal blood-gas partition coefficient	UF _C	composite uncertainty factor
Hb/g-H	human blood-gas partition coefficient	UF _D	database uncertainty factor
HEC	human equivalent concentration	UF _H	intraspecies uncertainty factor
HED	human equivalent dose	UF _L	LOAEL-to-NOAEL uncertainty factor
i.p.	intraperitoneal	UF _S	subchronic-to-chronic uncertainty factor
IRIS	Integrated Risk Information System	U.S.	United States of America
		WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV assessment.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ALUMINUM PHOSPHATE SALTS (MULTIPLE CASRNS)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund program. PPRTVs are derived after a review of the relevant scientific literature using established U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at <https://www.epa.gov/pprtv>. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing toxicologically relevant human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at <https://ecomments.epa.gov/chemicalsafety/>.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV assessment was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV assessment development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the toxicologically relevant effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV assessment used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at <https://ecomments.epa.gov/pprtv>.

1. INTRODUCTION

This document addresses the available data on the toxicity of aluminum phosphate salts. Aluminum phosphate salts are considered separately in this document from other inorganic phosphates (monovalent, divalent, and ammonium phosphates) because it is expected that the presence of aluminum would influence the chemistry, toxicokinetics, and/or toxicity of these salts relative to the other classes of inorganic phosphates. Specifically, the aluminum ions are expected to exert toxic effects that are independent of the phosphate moiety, which would confound the hazard identification for the other inorganic phosphates. The reader is referred to the PPRTV assessments for sodium/potassium salts of inorganic phosphates ([U.S. EPA, 2021d](#)), calcium salts of inorganic phosphates ([U.S. EPA, 2021c](#)), and ammonium phosphates ([U.S. EPA, 2021b](#)) for assessments of these inorganic phosphate salts, as well as the PPRTV assessment for aluminum ([U.S. EPA, 2006](#)).

Aluminum phosphate salts are inorganic salts composed of a phosphate anion and an aluminum cation. Aluminum phosphate (AlPO_4 , CASRN 7784-30-7) is a highly insoluble and unreactive compound consisting of aluminum (Al^{3+}) and phosphate (PO_4^{3-}) in a 1:1 ratio. Other complexes of aluminum phosphate, with varying ratios of aluminum and phosphoric acid groups (i.e., 3:1) and mixed sodium aluminum phosphates (SALPs), are also included in this assessment (see Table 1). These chemicals all contain aluminum (CASRN 7429-90-5). Aluminum is a metallic element with an atomic number of 13 and is a member of the post-transition metal series. Aluminum is the most abundant metallic element in the Earth's crust and is the most widely used nonferrous metal. Aluminum-containing compounds are widely distributed in rocks, soils, water, air, and food. In the environment and biological systems, aluminum is not found in the elemental form because of its chemical reactivity. Al^{3+} readily forms complexes with ligands, such as phosphates and metaphosphates, where phosphoric acid moieties form a cyclic (ring) structure, to counter the +3 charge.

Phosphorus (P) is most commonly found in nature in its pentavalent form in combination with oxygen, as phosphate (PO_4^{3-}). Phosphorus is an essential constituent of all living organisms, and is ubiquitous in most plant and animal tissues. Condensed (pyro-, meta-, and other) polyphosphates are formed when two or more orthophosphate molecules condense into a single molecule. Pyrophosphates refer to compounds with two condensed orthophosphates, and higher number polymers are termed polyphosphates, sometimes preceded by a prefix indicating the number (e.g., tri- and tetrapolyphosphates have three and four condensed phosphates, respectively). The term "metaphosphates" is used when phosphoric acid moieties form a cyclic (ring) structure. Inorganic phosphates (both ortho- and condensed phosphate anions) can be grouped into four classes based on their cations: monovalent (sodium, potassium, and hydrogen), divalent (calcium and magnesium), ammonium, and aluminum. The phosphoric acids have been grouped with the other monovalent cations based on valence state.

Aluminum phosphate occurs naturally as minerals such as berlinite (AlPO_4) or variscite (aluminum phosphate dihydrate [$\text{AlPO}_4 \cdot 2\text{H}_2\text{O}$]) ([Schrödter et al., 2012](#)). Aluminum phosphates are produced by combining alkali metal phosphates and solutions of aluminum salts or aluminum hydroxide with phosphoric acid ([Gilmour, 2019](#)). Aluminum phosphates are used in ceramics, cosmetics, paints, and varnishes and in paper and pulp industries ([ATSDR, 2008](#)). Human exposure to aluminum phosphates is expected based on their characterization as generally

recognized as safe (GRAS) for use as food additives, antacids, and as vaccine adjuvants by the U.S. Food and Drug Administration ([FDA, 1975](#)). Basic and acidic mixed SALPs are used in food applications, as emulsifying agents in pasteurized processed cheese, and as leavening agents in cereal foods, self-rising flour, prepared cake mixes, pancakes, waffles, and refrigerated or frozen dough or batter products ([ATSDR, 2008](#)). SALPs are food additives classified by the FDA as GRAS as a multiple-purpose food substance when used in accordance with good manufacturing practice under Chapter 21 of the Code of Federal Regulations ([FDA, 2020b](#)). The commercial product, Levair®, is an acidic form of SALP used as a leavening agent in food products and contains approximately 8% aluminum ([Hicks et al., 1987](#)). Levn Lite® is another acidic SALP that is used as a heat-triggered leavening agent in frozen foods and baking products (percentage aluminum unknown). Kasal™ and Kasal™II are dibasic forms of sodium phosphate containing approximately 6 and 13% aluminum, respectively. Kasal™ and Kasal™II are used in the production of cheese products ([Hicks et al., 1987](#)).

In 1974, the FDA announced that antacids containing aluminum compounds are GRAS for over-the-counter sale ([FDA, 1975](#)). The FDA has established a maximum daily dose of 8 g of aluminum phosphate gel for use as an antacid ([FDA, 2020a](#)). In general, antacids function by limiting the acid within the gastrointestinal tract from reaching the duodenum by neutralizing the acid present in the stomach. Available information on aluminum-containing antacids applies mostly to aluminum hydroxide gel, which is reported to function by the aluminum binding with dietary phosphorus and impairing gastrointestinal absorption of phosphorus ([Spencer and Lender, 1979](#)). The mechanism of acid neutralization is expected to vary for each salt ([Salisbury and Terrell, 2020](#)).

The FDA has also licensed aluminum salts (aluminum hydroxide, aluminum phosphate, and potassium aluminum sulfate) to be used as an adjuvant in many vaccines ([ATSDR, 2008](#)). Aluminum salt adjuvants form an insoluble depot that slowly releases the antigen, which stimulates an antibody response. Clinical studies have demonstrated that aluminum enhances the antigenicity of certain vaccines ([Baylor et al., 2002](#)). The amount of aluminum permitted within an individual dose of a biological product cannot exceed 0.85 mg if determined by assay, or 1.14 mg if determined by calculation on the basis of the amount of aluminum compound added ([FDA, 2020b](#)). Aluminum adjuvants have been associated with severe local reactions in some people ([ATSDR, 2008](#); [Baylor et al., 2002](#)).

The empirical formulas for several aluminum and mixed SALPs are shown in Table 1. Table 1 also summarizes available information on the physicochemical properties of these compounds; limited information is available for most of them. Several of these compounds (CASRN 13776-88-0, 13939-25-8, 13530-50-2, and 7785-88-8) are listed in the U.S. EPA's 2019 Toxic Substance and Chemical Act (TSCA) public inventory ([U.S. EPA, 2021e](#)), and several (CASRN 7784-30-7, 13776-88-0, 13939-25-8, 13530-50-2, 7785-88-8, and 15136-87-5) are registered or preregistered in Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program ([ECHA, 2019a, b, c, d, e, f](#)). Repeated-dose toxicity information in the European Chemicals Agency (ECHA) is based on an analogue (read-across) approach using available data on oral exposures to SALPs, along with available supporting information. This approach was based on the common functional groups of the Al³⁺ cation and the PO₄³⁻ anion, the likelihood of these common breakdown products, and similarities in solubilities.

Table 1. Identity, Molecular Weight, and Physicochemical Properties of Aluminum Phosphates and Mixed Sodium Aluminum Phosphates Considered in this Assessment^a

Compound [synonym]	CASRN	Molecular Formula ^b	MW (g/mol) ^b	MW Ratio P:Compound ^c	Physical State	Melting Point (°C)	Density (g/cm ³ at 25°C)	Solubility in Water
Phosphoric acid, aluminum salt (1:1) [aluminum phosphate]	7784-30-7	AlO ₄ P	121.951	0.25399	White crystals ^d	1,500 ^d	2.566 ^d	Insoluble in water, ^d slightly soluble at low pH
Metaphosphoric acid (HPO ₃), aluminum salt (3:1) [aluminum metaphosphate]	13776-88-0	AlO ₉ P ₃	263.894	0.35212	White powder ^d	1,527 ^d	NV	Insoluble in water ^d
Triphosphoric acid, aluminum salt (1:1) [aluminum triphosphate]	13939-25-8	AlH ₂ O ₁₀ P ₃	281.909	0.32962	NV	NV	NV	Insoluble in water ^e
Phosphoric acid, aluminum salt (3:1) [monoaluminum phosphate; aluminum dihydrogen phosphate]	13530-50-2	AlH ₆ O ₁₂ P ₃	317.939	0.29226	White powder ^f	NV	NV	Soluble in unbuffered water (294 g Al/L at pH 2 at 20°C); low solubility in buffered water (5,535.5 µg Al/L at pH 6; 6.293 µg Al/L at pH 8) ^g
Phosphoric acid, aluminum sodium salt (8:3:1), tetrahydrate [sodium aluminum phosphate tetrahydrate (SALP)]	10305-76-7	Al ₃ H ₂₂ NaO ₃₆ P ₈	949.864	0.26087	NV	NV	NV	Insoluble in water ^h
Phosphoric acid, aluminum sodium salt (8:2:3) [sodium aluminum phosphate anhydrous (basic SALP)]	10279-59-1	Al ₂ H ₁₅ Na ₃ O ₃₂ P ₈	897.81	0.27600	White powder ^d	NV	NV	Sparingly soluble in water ⁱ
Phosphoric acid, aluminum sodium salt (1:?:?) [sodium aluminum phosphate acidic (acidic SALP)]	7785-88-8	Mixture of Al ₃ H ₂₂ NaO ₃₆ P ₈ and Al ₂ H ₁₅ Na ₃ O ₃₂ P ₈	NA	NA	White powder ^d	NV	NV	Insoluble in water ^d

Table 1. Identity, Molecular Weight, and Physicochemical Properties of Aluminum Phosphates and Mixed Sodium Aluminum Phosphates Considered in this Assessment^a

Compound [synonym]	CASRN	Molecular Formula ^b	MW (g/mol) ^b	MW Ratio P:Compound ^c	Physical State	Melting Point (°C)	Density (g/cm ³ at 25°C)	Solubility in Water
Phosphoric acid, aluminum sodium salt (8:3:1) [trialuminum sodium tetra-decahydrogenoctaorthophosphate]	15136-87-5	Al ₃ H ₁₄ NaO ₃₂ P ₈	877.804	0.28229	NV	NV	NV	Insoluble in water ⁱ

^aOctanol-water partition coefficient, Henry's law constant, soil adsorption coefficient (K_{oc}), atmospheric OH rate constant, and atmospheric half-life are not applicable to aluminum phosphates.

^bData were extracted from the U.S. EPA CompTox Chemicals Dashboard: aluminum phosphate salts, multiple CASRN; <https://comptox.epa.gov/dashboard>; accessed December 18, 2019. Data presented are experimental averages unless otherwise noted (U.S. EPA, 2021a).

^cMW of P = 30.974 g/mol (NLM, 2021b).

^dLarrañaga et al. (2016).

^eECHA (2019a).

^fU.S. EPA (2015).

^gECHA (2019c).

^hEU (2012).

ⁱIOM (2003).

MW = molecular weight; NA = not applicable; NV = not available; P = phosphorus; SALP = sodium aluminum phosphate; U.S. EPA = U.S. Environmental Protection Agency.

As shown in Table 1, aluminum phosphate salts are largely insoluble in water and sparingly soluble under acidic conditions ([Schrödter et al., 2012](#); [ATSDR, 2008](#)). Free aluminum (Al^{3+}) forms an insoluble salt with phosphate (AlPO_4 ; $\text{AlPO}_4 \cdot 2\text{H}_2\text{O}$) within the pH range of 5–6 ([ATSDR, 2008](#)). Aluminum tris(aluminum dihydrogen phosphate) (CASRN 13530-50-2) demonstrated high solubility in unbuffered water, where the final pH value of the solution was 2 ([ECHA, 2019c](#)). The pH of the water decreased with increased loading of the aluminum tris(dihydrogen phosphate) test substance. However, in buffered solutions at pH 6 and 8, this compound demonstrated low solubility. Under acidic conditions, like those found in parts of the digestive system, Al^{3+} is expected to be the dominant species ([Martin, 1986](#)). However, due to the low solubility of aluminum phosphates at biological pHs, the “free” aluminum ions occur in very low concentrations ([ATSDR, 2008](#)). Although bioavailability appears to generally parallel water solubility, data are insufficient to fully inform this extrapolation ([ATSDR, 2008](#)). Bioavailability in the human body is a function of the chemical form that occurs in the gastrointestinal tract (i.e., forming of complexes with dietary ligands). By comparison to other aluminum salts (i.e., aluminum hydroxide), aluminum phosphates have a lower tendency to be solubilized in the presence of dietary acids and a lower tendency to form absorbable complexes ([Berthon and Daydé, 1992](#)).

A summary of available toxicity values for aluminum phosphates from the U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values Relevant to Aluminum Phosphates (Multiple CASRNs)				
Source (parameter)^{a,b}		Value (applicability)	Notes	Reference^c
Noncancer				
IRIS		NV	NA	U.S. EPA (2019)
PPRTV (RfD, chronic)	Aluminum	1 mg Al/kg-d	Based on a LOAEL of 100 mg Al/kg-d for minimal neurotoxicity in the offspring of mice.	U.S. EPA (2006)
HEAST		NV	NA	U.S. EPA (2011b)
DWSHA		NV	NA	U.S. EPA (2018)
ATSDR (MRL, oral intermediate)	Aluminum	1 mg Al/kg-d	Based on a NOAEL of 26 mg Al/kg-d for neurodevelopmental effects in mice.	ATSDR (2019) ; ATSDR (2008)
ATSDR (MRL, oral chronic)	Aluminum	1 mg Al/kg-d	Based on decreases in forelimb and hindlimb grip strength and thermal sensitivity in a chronic study in mice.	ATSDR (2019) ; ATSDR (2008)

Table 2. Summary of Available Toxicity Values Relevant to Aluminum Phosphates (Multiple CASRNs)				
Source (parameter)^{a,b}		Value (applicability)	Notes	Reference^c
IOM (UL)	Phosphate	Children: 3,000 mg P/d Adults ≤70 yr: 4,000 mg P/d Adults >70 yr: 3,000 mg P/d Pregnant women: 3,500 mg P/d Lactating women: 4,000 mg P/d	The maximum level of daily P intake that is likely to pose no risk of toxicologically relevant effects. The UL represents total intake from food, water, and supplements.	IOM (1997)
WHO (MTDI)	Phosphate	70 mg P/kg body weight	Maximum intake of P across all sources; based on nephrocalcinosis in rats.	IPCS (2019) ; WHO (1982)
CalEPA		NV	NA	CalEPA (2019) ; CalEPA (2001)
OSHA		NV	NA	OSHA (2018a) ; OSHA (2018b) ; OSHA (2018c)
NIOSH		NV	NA	NIOSH (2018)
ACGIH (TLV-TWA, respirable particulate matter)	Aluminum metal and insoluble compounds	1 mg/m ³	Based on pneumoconiosis, lower respiratory tract irritation, and neurotoxicity.	ACGIH (2018) ; ACGIH (2008)
DOE (PAC)	Aluminum phosphate (CASRN 7784-30-7)	PAC-1: 14 mg/m ³ PAC-2: 200 mg/m ³ PAC-3: 1,200 mg/m ³	PAC-1 based on MW-adjusted insoluble aluminum (CASRN 7429-90-5) TLV-TWA, PAC-2 based on TEEL-3, and PAC-3 based on rat oral LDLo.	DOE (2018)
DOE (PAC)	Aluminum tris(dihydrogen phosphate) (CASRN 13530-50-2)	PAC-1: 3 mg/m ³ PAC-2: 33 mg/m ³ PAC-3: 200 mg/m ³	PAC-1 based on insoluble aluminum (CASRN 7429-90-5) TLV-TWA, PAC-2 based on TEEL-1, and PAC-3 based on TEEL-2.	DOE (2018)
USAPHC (air-MEG)	Aluminum phosphate (CASRN 7784-30-7)	1-h critical: 500 mg/m ³ 1-h marginal: 500 mg/m ³ 1-h negligible: 100 mg/m ³	Based on TEELs.	U.S. APHC (2013)
USAPHC (air-MEG)	Aluminum phosphate solution (CASRN 13530-50-2)	1-h critical: 300 mg/m ³ 1-h marginal: 60 mg/m ³ 1-h negligible: 60 mg/m ³	Based on TEELs.	U.S. APHC (2013)

Table 2. Summary of Available Toxicity Values Relevant to Aluminum Phosphates (Multiple CASRNs)				
Source (parameter)^{a,b}		Value (applicability)	Notes	Reference^c
Cancer				
IRIS		NV	NA	U.S. EPA (2019)
HEAST		NV	NA	U.S. EPA (2011b)
DWSHA		NV	NA	U.S. EPA (2018)
NTP		NV	NA	NTP (2016)
IARC		NV	NA	IARC (2019)
CalEPA		NV	NA	CalEPA (2019)
ACGIH (WOE)	Aluminum metal and insoluble compounds	A4: Not classifiable as a human carcinogen	Based on no evidence that aluminum compounds are carcinogenic except on implantation in animals, a route of exposure that is not relevant to occupational exposure.	ACGIH (2018) ; ACGIH (2008)

^aSources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IOM = Institute of Medicine; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PPRTV = Provisional Peer-Reviewed Toxicity Value; USAPHC = U.S. Army Public Health Command; WHO = World Health Organization.

^bParameters: LOAEL = lowest-observed-adverse-effect level; MEG = military exposure guideline; MRL = minimum risk level; MTDI = maximum tolerable daily intake; NOAEL = no-observed-adverse-effect level; PAC = protective action criteria; RfD = reference dose; TEEL = temporary emergency exposure limit; TLV = threshold limit value; TWA = time-weighted average; UL = tolerable upper intake level; WOE = weight of evidence.

^cReference date is the publication date for the database and not the date the source was accessed.

Al = aluminum; LDLo = lowest reported lethal dose; MW = molecular weight; NA = not applicable; NV = not available; P = phosphorus.

Literature searches were conducted in April–June 2019 and updated most recently in January 2023 for studies relevant to the derivation of provisional toxicity values for the eight aluminum phosphate compounds shown in Table 1 above: aluminum phosphate (CASRN 7784-30-7), aluminum metaphosphate (CASRN 13776-88-0), aluminum triphosphate (CASRN 13939-25-8), monoaluminum phosphate (CASRN 13530-50-2), sodium aluminum phosphate tetrahydrate (SALP, CASRN 10305-76-7), sodium aluminum phosphate anhydrous (basic SALP, CASRN 10279-59-1), sodium aluminum phosphate acidic (acidic SALP, CASRN 7785-88-8), and trialuminum sodium tetra decahydrogenooctaoorthophosphate (CASRN 15136-87-5). Searches were conducted using the U.S. EPA’s Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the

following databases: PubMed, TOXLINE¹ (including TSCATS1), Scopus, and Web of Science. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), the U.S. EPA Chemical Data Access Tool (CDAT), the U.S. EPA ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, the U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

¹TOXLINE content was migrated to PubMed (<https://www.nlm.nih.gov/databases/download/toxlinesubset.html>); therefore, it was not included in the literature search update from March 2022.

2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer evidence bases, respectively, for aluminum phosphate salts and include all potentially relevant repeated-dose short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. The phrase “statistical significance” and term “significant,” used throughout the document, indicate a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Data for Aluminum Phosphate Salts (Multiple CASRNs)							
Category ^a	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m³)							
ND							
Animal							
1. Oral (mg/kg-d)							
Short-term	25 M/0 F, Sprague Dawley, rat, oral in feed (corn oil vehicle), 28 d Reported analytical concentrations: 0, 30,000 (Kasal TM), 7,000, or 30,000 ppm (Kasal TM II)	0, 2,436 (Kasal TM), 0, 558, 2,471 (Kasal TM II)	No toxicologically relevant effects in males.	2,471	NDr	Hicks et al. (1987)	PR
Subchronic	15 M/15 F, albino, rat (strain NR), oral in feed, 90 d Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Kasal TM	0, 172.66, 562.74, 1,803.11 (M) 0, 205.62, 701.32, 2,113.79 (F)	No toxicologically relevant effects in males. Dose-related increase in incidence and severity of nephrocalcinosis in females; increased relative kidney weight in high-dose females.	1,803.11 (M)* NDr (F)*	NDr (M)* 205.62 (F)*	Anonymous (1972) as cited in ECHA (1972e) (Limited study details are available; FDA (1975) reported that the study was performed by IBT.*)	NPR, SS

Table 3A. Summary of Potentially Relevant Data for Aluminum Phosphate Salts (Multiple CASRNs)

Category ^a	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Subchronic	15 M/15 F, albino, rat (strain NR), oral in feed, 90 d Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Levair®	0, 182.57, 594.65, 1,909.53 (M) 0, 210.09, 693.99, 1,988.42 (F)	No toxicologically relevant effects in males. Dose-related increase in incidence of nephrocalcinosis in females.	1,909.53 (M)* NDr (F)*	NDr (M)* 210.09 (F)*	Anonymous (1972) as cited in ECHA (1972f) (Limited study details are available; FDA (1975) reported that the study was performed by IBT.*)	NPR, SS
Subchronic	15 M/15 F, albino, rat (strain NR), oral in feed, 90 d Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Levn Lite®	0, 155.36, 545.64, 1,796.95 (M) 0, 181.18, 701.65, 2,070.10 (F)	No toxicologically relevant effects in males. Dose-related increase in incidence of nephrocalcinosis in females; increased relative kidney weight in high-dose females.	1,796.95 (M)* NDr (F)*	NDr (M)* 181.18 (F)*	Anonymous (1972) as cited in ECHA (1972c) (Limited study details are available; FDA (1975) reported that the study was performed by IBT.*)	NPR, SS
Subchronic	15 F, albino, rat (strain NR), oral in feed, 90 d Reported analytical concentrations: 0, 300, or 1,000 ppm Levn Lite®	0, 18.1, 70.17, (F)	Decreased absolute kidney weight by 23 and 24% in low- and high-dose females, respectively. Decreased relative kidney weight by 6% in both treated groups.	NDr (F)*	NDr (F)*	Anonymous (1972) as cited in ECHA (1973) (Limited study details are available.)	NPR, SS

Table 3A. Summary of Potentially Relevant Data for Aluminum Phosphate Salts (Multiple CASRNs)

Category ^a	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Subchronic	4 M/4 F, beagle, dog, oral in feed, 90 d Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Kasal™	0, 94.23, 322.88, 1,107.12 (M) 0, 129.31, 492.77, 1,433.56 (F)	Renal tubular concretions of moderate severity observed in 2/4 males and 1/4 females at the high dose.	322.88 (M)* 492.77 (F)*	1,107.12 (M)* 1,433.56 (F)*	Anonymous (1972) as cited in ECHA (1972a) (Limited study details are available; FDA (1975) reported that the study was performed by IBT.*)	NPR, SS
Subchronic	4 M/4 F, beagle, dog, oral in feed, 90 d Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Levn Lite®	M: 0, 94.55, 345.21, 1,038.77 F: 0, 118.66, 511.06, 1,460.76	No toxicologically relevant effects were observed in either sex.	1,038.77 (M)* 1,460.76 (F)*	NDr (M)* NDr (F)*	Anonymous (1972) as cited in ECHA (1972d) (Limited study details are available; FDA (1975) reported that the study was performed by IBT.*)	NPR, SS
Subchronic	6 M/6 F, beagle, dog, oral in feed (corn oil vehicle), 6 mo Reported analytical concentrations: 0, 0.3, 1.0, or 3.0% Levair®	0, 118, 317, 1,034 (M) 0, 112, 361, 1,087 (F)	No toxicologically relevant effects were observed in either sex.	1,034 (M) 1,087 (F)	NDr	Katz et al. (1984) (GLP-compliant, OECD 422 guideline study.)	PR

Table 3A. Summary of Potentially Relevant Data for Aluminum Phosphate Salts (Multiple CASRNs)

Category ^a	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Subchronic	4 M/4 F, beagle, dog, oral in feed (corn oil vehicle), 6 mo Reported analytical concentrations: 0, 3,000, 10,000, or 30,000 ppm Kasal™	0, 112, 390, 1,143 (M) 0, 106, 323, 1,251 (F)	High-dose males experienced sharp decreases in food consumption and body weight near the end of the study, presumably reflecting an unexplained problem with the food, health, or handling of the animals in that group at that time. Disregarding effects likely secondary to the abrupt decrease in food consumption, the high dose is tentatively identified as a LOAEL in males for mild liver (hepatocyte vacuolation and hypertrophy) and kidney (tubular-glomerulonephritis) lesions of uncertain relation to the drop in food consumption and body weight. No toxicologically relevant effects in females.	390 (M) 1,251 (F)	1,143 (M) NDr (F)	Pettersen et al. (1990) , Anonymous (1987) as cited in ECHA (1987)	PR
Reproductive/ Developmental	10 breeding pairs/group, Crj:CD(SD)IGS, rat, gavage, 46 d beginning 14 d prior to mating (M), 14 d prior to mating to PND 4 (F) Reported analytical concentrations: 0, 100, 300, or 1,000 mg/kg-d triphosphoric acid aluminum salt (K-Fresh 100P)	0, 100, 300, 1,000	Parental: No toxicologically relevant effects. Pups: No toxicologically relevant effects.	1,000	NDr	Anonymous (2002) as cited in ECHA (2002d) (GLP-compliant, OECD 422 guideline study.)	NPR, SS

Table 3A. Summary of Potentially Relevant Data for Aluminum Phosphate Salts (Multiple CASRNs)

Category ^a	Number of Male/Female, Strain, Species, Exposure Route, Reported Doses, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	LOAEL ^b	Reference (comments)	Notes ^c
2. Inhalation (mg/m³)							
ND							

^aDuration categories are defined as follows: acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) ([U.S. EPA, 2002](#)).

^bDosimetry: doses are presented as ADDs (mg/kg-day) for oral noncancer effects.

^cNotes: NPR = not peer reviewed; PR = peer reviewed; SS = available only as reported in secondary source.

*These effect levels are tentative and for comparative purposes only. The reported data are not considered by the U.S. EPA to be a suitable basis for quantitative evaluation. There is low confidence in this study, due to demonstrated poor reliability of the performing laboratory (IBT) and limitations of the available secondary source (see Section 2.2.1 for details).

ADD = adjusted daily dose; F = female(s); GLP = Good Laboratory Practice; IBT = Industrial Bio-Test Laboratories, Inc.; Kasal™ = basic SALP containing approximately 6% aluminum; Kasal™II = basic SALP containing 13% aluminum; Levair® = an acidic SALP from Staffer Chemical Company; Levn Lite® = an acidic SALP formulation from Monsanto Company (Solutia Inc.); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NR = not reported; OECD = Organisation for Economic Co-operation and Development; PND = postnatal day; SALP = sodium aluminum phosphate; U.S. EPA = U.S. Environmental Protection Agency.

Table 3B. Summary of Potentially Relevant Cancer Data for Aluminum Phosphate Salts (Multiple CASRNs)					
Category	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry	Critical Effects	Reference (comments)	Notes
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m³)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m³)					
ND					

ND = no data.

2.1. HUMAN STUDIES

2.1.1. Oral Exposures

Data in humans following oral exposure to aluminum phosphate come from a single study that evaluated the safety of aluminum phosphate gel (as an antacid treatment) in the short-term treatment of duodenal ulcer ([Parente et al., 1995](#)). In this study, 153 patients with endoscopically proven active duodenal ulcer received 11 g of aluminum phosphate gel 5 times daily for 6 weeks. At the end of treatment, 74 out of 113 patients (65%) who completed the study showed ulcer healing, although constipation was reported as a side effect of the treatment.

2.1.2. Inhalation Exposures

No studies of humans exposed to aluminum phosphate salts by inhalation have been identified in the literature searches or secondary sources reviewed.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

Short-Term Studies

[Hicks et al. \(1987\)](#)

A 28-day repeated-dose study in rats was performed by [Hicks et al. \(1987\)](#). This study evaluated the effects of dietary exposure to two separate samples of commercial food-grade basic SALP, Kasal™ (contains approximately 6% aluminum as reported by the study authors) and Kasal™II (contains approximately 13% aluminum as reported by the study authors). Forty-eight-day-old male Sprague Dawley rats (25/group) were fed basal diets (Purina certified rat chow no. 5002) or diets containing nominal concentrations of 30,000 ppm Kasal™ or 7,000 or 30,000 ppm Kasal™II for 28 days. Measured dietary concentrations were within 5% of nominal. Reported average daily doses of Kasal™ were 0 or 2,436 mg/kg-day. Reported average daily doses of Kasal™II were 0, 558, or 2,471 mg/kg-day. A fifth group of animals serving as a positive control was similarly dosed with 14,470 ppm (1,139 mg/kg-day) of aluminum hydroxide. A corn oil (0.5% weight) vehicle was used for all diet preparations. Animals were observed twice daily for clinical signs, behavior (details not specified), and mortality. General physical examinations were performed weekly. Food consumption and body weights were measured for 10 rats/group and water consumption was measured for 5 rats/group, weekly.

After 28 days of treatment, 15 rats/group were sacrificed. At sacrifice, blood from five rats/group was collected for hematology (hematocrit, hemoglobin concentration, erythrocyte count, total and differential leucocyte count, and platelet count) and serum chemistry (alanine aminotransferase [ALT], alkaline phosphatase [ALP], blood urea nitrogen [BUN], creatinine, phosphorus, sodium, chloride, and potassium) measurements. Brain, liver, kidneys, and testes from sacrificed animals were weighed. Tissues from select organs (not specified) were fixed for histological analysis (five per group). Femurs from five animals/group were analyzed for aluminum concentration. The remaining rats from all groups were placed on basal diets for a 2-month (five per group) or 5-month (five per group) recovery period. Femurs from these animals were collected for aluminum analysis. No gross or microscopic examinations were performed on recovery animals. The Dunnett's test was used to identify significant changes in body weights, food consumption, hematology, clinical chemistry parameters, and organ weights. The Mann-Whitney U-Test was used on nonparametric data. The Mantel-Haenszel test was used to identify trends in incidence data, followed by χ^2 analysis or Fisher's exact test. Data were considered significant at $p < 0.05$.

Data for several endpoints (clinical signs, body weights, food and water consumption, hematology, organ weights, and gross examinations) were not provided in the published report, and were therefore not available for independent review. Clinical signs, including abrasions, scabs, and sporadic incidences of chromorhinorrhea, chromodacryorrhea, hair loss, and dehydration were reported to occur similarly across all groups. There were no apparent changes in body weights or in food or water consumption throughout treatment or during the recovery periods. Hematological endpoints were reported to be similar across all groups. Serum chemistry measurements were reported, and statistically significant increases in plasma sodium levels were observed in all treatment groups (including animals treated with aluminum hydroxide), compared with controls (see Table B-1). However, the magnitudes of change in serum sodium levels compared to controls were small (2–4%) and values fell within the range of historical control values. A significant 16% increase compared to controls in absolute kidney weight was reported by the study authors in the 558 mg/kg-day group (low-dose Kasal™II), but there were no increases in relative kidney weight at this dose or any significant changes at the higher dose (data not provided).

The study authors reported no gross pathology findings at autopsy related to treatment. No significantly increased incidences of microscopic lesions were observed, although the number of animals examined was small ($n = 5$) (see Table B-2). Mild to moderate focal myocardial degeneration was observed in one to three rats in all groups, including controls. Observed renal lesions in all groups included focal cystic changes, pelvic dilation, membranous glomerulonephropathy, hyaline-droplet degeneration of proximal tubes, hyperplasia of pelvic transitional epithelium, and focal lymphocytic inflammation. Two control rats and one rat treated with 2,436 mg/kg-day of Kasal™ exhibited moderate degeneration of the testicular seminiferous tubules. Aluminum concentrations in the femur did not appreciably change from controls in any treatment group, including aluminum hydroxide, and was at or below the limit of detection in several animals.

A no-observed-adverse-effect level (NOAEL) of 2,471 mg/kg-day, the highest dose, was determined based on the lack of treatment-related effects in male Sprague Dawley rats administered Kasal™ or Kasal™II (basic SALP) in the diet for 28 days.

Subchronic Studies

Industrial Bio-Test Laboratories Studies

As described by [FDA \(1975\)](#), Industrial Bio-Test Laboratories, Inc. (IBT) evaluated three commercial SALP products for two separate producers in a series of studies performed in rats and dogs. IBT has been identified by OECD as an unreliable source of laboratory data.² In addition, descriptions of study findings are based on a limited summary from a secondary source.

²In its manual for assessment of HPV chemicals, [OECD \(2019\)](#) noted that 618 of 867 nonacute toxicity studies conducted by IBT (including subacute, subchronic, carcinogenicity, reproductive toxicity, genotoxicity, and neurotoxicity studies) were found to be invalid during a post hoc audit program conducted by the U.S. EPA and the Canadian Health and Welfare Department. [OECD \(2019\)](#) outlines specific criteria for using data generated by IBT and recommends rejecting a study when either a regulatory or internal (IBT) audit revealed problems impacting the reliability of the findings or when the findings of unaudited studies are inconsistent with data collected later by reputable laboratories. [OECD \(2019\)](#) recommends that studies that have not been audited should be used with caution and only as weak evidence if supported by later data from reputable laboratories.

The studies are described here because they constitute much of the available database for aluminum phosphate salts. There is, however, low confidence in the reported results.

In 1972, 90-day feeding studies in rats and dogs were performed evaluating the effects of oral exposure to Kasal™ (basic SALP) and Levair® (an acidic SALP from Stauffer Chemical Company) and Levn Lite® (an acidic SALP formulation from Monsanto Company [Solutia Inc.]). Full study reports are not available, but there are study summaries in ECHA that correspond to the 90-day dietary rat study of Kasal™, Levair®, and Levn Lite® [Anonymous (1972) studies as cited in [ECHA \(1972c, 1972e, 1972f\)](#)] and to the 90-day dietary dog study of Kasal™ and Levn Lite® [Anonymous (1972) studies as cited in [ECHA \(1972a, 1972d\)](#)]. No study summary was located corresponding to the 90-day dietary study of Levair® in dogs. For the rats, the summaries in ECHA share the same methodological details and matching control data, suggesting that only a single negative control group was used. It was, therefore, presumed that the three commercial SALP products were evaluated as a single study in rats. Similarly for the dogs, the summaries in ECHA share the same methodological details and matching control data, suggesting that only a single negative control group was used, and exposures to both Kasal™ and Levn Lite® were evaluated as a single study in dogs.

For the purposes of this assessment, the studies are summarized below for rats first and then for dogs. Methodological details, which apply to exposures for all the commercial formulations evaluated, are presented first, followed by the results for each of the formulations tested in sequence.

Industrial Bio-Test Laboratories, Inc. 90-Day Feeding Study in Rats

The doses selected for the 90-day feeding study in rats appear to have been based on the results of a 30-day pilot study summarized in ECHA [Anonymous (1972) as cited in [ECHA \(1972b\)](#)]. In this dose range-finding study, groups of commercially obtained albino rats (5/sex/dose, strain and age not specified) were fed ad libitum diets that contained 0 (plain diet), 1.0, 3.0, 5.0, or 7.0% nominal concentrations of the three test materials, Kasal™, Levair®, or Levn Lite® (each separately), for 30 days. Details of the composition and purity of the test materials were not provided. For the pilot study, rats were only evaluated for changes in body weights and food consumption. Body weights of each animal were measured on the first day of the test and weekly thereafter. Food consumption data were collected weekly. Weekly body weight and food consumption data were not provided in the study summary, but a table summarizing the mean 30-day weight gains and food consumptions was provided. In brief, depressions in weight gains and food intake were noted in groups fed diets containing 5.0 or 7.0% nominal concentrations of Levair®, Kasal™, and Levn Lite®. Based on the results of this study, dietary levels of 0.3, 1.0, and 3.0% were selected for the 90-day rat study.

The 90-day study predated (1972) established OECD guidelines and Good Laboratory Practices (GLP). Groups of commercially obtained albino rats (15/sex/dose, strain and age not specified) were fed continuous diets that contained no test material (plain diet), or 0.3, 1.0, or 3% of Kasal™, Levair®, or Levn Lite® for 90 days [Anonymous (1972) studies as cited in [ECHA \(1972c, 1972e, 1972f\)](#)]. Doses (as noted below) of each commercial product were reported in the individual ECHA summaries, calculated using the mean of the weekly body weight and food consumption data. The purity of Levair® [$\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$] was reported to be 99.9%; details of the composition and purity of the other two test materials were not provided. Animals were observed daily for clinical signs. Body weights (all animals) and food consumption

(5/sex/group) were recorded weekly. The methodology (“Examinations”) sections in the ECHA summaries for Kasal™ and Levair® simply noted that hematology, clinical chemistry, urinalysis, gross pathology, and histopathology were performed, without providing additional details. The study summary for the Levn Lite® study indicated that hematology (hematocrit, erythrocyte count, hemoglobin, and total and differential leukocyte counts), limited clinical chemistry (BUN, fasted glucose, ALP, and ALT), and urine endpoints (glucose, albumin, microscopic elements, pH, and specific gravity) were measured in 10 control and 10 high-dose males and females on Study Days 45 and 84. All surviving rats were sacrificed at the end of the 90-day feeding period. Animals were grossly examined at sacrifice. Organ weight measurements were limited to the liver, kidneys, spleen, gonads, heart, and brain of each rat.

The Levn Lite® summary stated that the microscopic examination of tissues was performed for 10 rats/sex from the control and high-dose group on esophagus, stomach, small intestine, cecum, colon, liver, kidneys, spleen, pancreas, urinary bladder, pituitary gland, adrenal gland, testes, seminal vesicle, ovary, bone marrow, thyroid gland, parathyroid gland, salivary gland, prostate gland, heart, aorta, lung, lymph nodes, skeletal muscle, peripheral nerve, bone (femur), spinal cord, uterus, trachea, eye, optic nerve, and brain. Results (for all formulations), however, were provided for all dose groups and indicated that there were 15 female rats evaluated from the low-dose groups (10 rats/sex for other dose groups). The endpoints that were analyzed statistically are unclear. Except for organ weight data, no statistical analysis was included in the available data tables. Organ-weight data were analyzed for variance using analysis of variance (ANOVA) followed by *t*-tests to identify statistical significance. Measures of variance (e.g., standard deviation [SD] or standard error [SE]) were not included in any of the data tables. For clarity, results for each commercial product are reported separately below. However, the data tables in Appendix B include values for all three formulations for a given endpoint to facilitate comparisons across the three SALP products.

Kasal™

Doses of Kasal™ were reported as 0, 172.66, 562.74, and 1,803.11 mg/kg-day for male rats and 0, 205.62, 701.32, and 2,113.79 mg/kg-day for female rats [Anonymous (1972) as cited in [ECHA \(1972e\)](#)]. No animals in the Kasal™ treatment groups died. Details of cage-side observations were not included in the available summary. It was reported that no effects on body weights, body-weight gain, or food consumption were seen; data for these endpoints were not available for independent review. Mean values without measures of variance were provided for hematological, clinical chemistry, and urinalysis endpoints in control and high-dose groups. Hematology measurements showed 15, 18, and 120% increases in neutrophil, monocyte, and eosinophil cell counts, respectively, in high-dose males compared with controls (see Table B-3). Changes in females included 10–11% decreases in neutrophils and eosinophils and a 30% increase in monocytes. No measures of variance or statistical analyses were provided; therefore, the significance of these changes is unclear. Several animals in all groups, including controls, were reported to have chronic murine pneumonia, and/or chronic tracheitis, indicating that animals in this study were potentially in poor general health. The available study summary indicated that no serum biochemistry effects were observed, although again, no measures of variance or statistical analyses were provided. The data showed a 21% decrease in ALP in high-dose male rats and a 42% increase in ALP and 14% increase in BUN in high-dose female rats, compared with controls (see Table B-4). No notable changes in the urine endpoints examined were observed.

The only statistically significant organ weight change in males treated with Kasal™ compared to controls was a 15% increase in absolute liver weight in the lowest dose group (see Table B-5). Relative liver-to-body and liver-to-brain weights were increased at this dose by 10–11% (not a statistically significant increase), but not at higher doses. In female rats, a statistically nonsignificant 12% increase in absolute kidney weight, compared with controls, and statistically significant increases of 16 and 14% in kidney weights relative to body and brain weight, respectively, were seen in the high-dose group. No changes in kidney weights were observed in the lower dose groups. Absolute and relative liver weights were significantly increased 16–23% in the low-dose females, but not in the higher dose groups. The study summary did not include all histological data, but rather presented limited data for the lesions that were observed, most notably a dose-related increase in the incidence of microconcretions in the renal tubules (nephrocalcinosis) of female rats. The data table presented in the study summary does not specifically note incidence of this lesion within controls. However, the conclusion section stated that these microconcretions were absent in the control animals. Thus, the incidences of microconcretions in female rats fed diets containing Kasal™ were 0/10, 4/15, 3/10, and 8/10 in the control, low-, mid-, and high-dose groups, respectively (see Table B-6). The severity of these lesions increased from minimal in the low-dose animals to mild in the mid- and high-dose animals. Similar lesions were not observed in male rats. Focal interstitial nephritis occurred in 2/10 high-dose males but was not observed in females. Other kidney lesions, including tubular nephrosis, chronic nephritis, and focal lymphoid infiltration, occurred at low incidences in a non-dose-related manner. Non-neoplastic findings in other organs did not appear to be treatment-related (i.e., incidences of chronic pneumonia and tracheitis in several animals, including controls).

As noted above, there is low confidence in this study, based on availability only as a limited summary from a secondary source and demonstrated poor reliability of the performing laboratory (IBT). For this reason, the reported data are not considered by the U.S. EPA to be a suitable basis for quantitative evaluation. Tentative effect levels are identified here for comparative purposes only. In female rats, the low dose of 205.62 mg Kasal™/kg-day is tentatively identified as a lowest-observed-adverse-effect level (LOAEL), based on the dose-related increase of microconcretions in the renal tubules, and a NOAEL was not determined. For male rats, the high dose of 1,803.11 mg Kasal™/kg-day is tentatively identified as a NOAEL, based on the lack of toxicologically relevant treatment-related effects following dietary exposure to Kasal™ for 90 days, and no LOAEL was determined.

Levair®

Doses of Levair® were reported as 0, 182.57, 594.65, and 1,909.53 mg/kg-day for male rats and 0, 210.09, 693.99, and 1,988.42 mg/kg-day for female rats [Anonymous (1972) as cited in [ECHA \(1972f\)](#)]. Four animals treated with Levair® died (sex and treatment groups were not specified). All deaths were attributed to trauma incurred during collection of blood samples. It was reported that no unexpected behavioral changes occurred and there were no effects on body weights, body-weight gain, or food consumption; data for these endpoints were not available for independent review. There was a 24% increase in monocytes in high-dose males and a 50% increase in monocytes in high-dose females, compared with controls (see Table B-3), but the significance of these changes is unclear, as variance data were not shown and statistical analyses were not performed. Other hematological changes were unremarkable. Compared to controls, high-dose females exhibited a 58% increase in ALP activity (see Table B-4), but again, the significance of this change is uncertain without statistical analysis or variance data. No serum

chemistry changes in males and no changes in urinalysis parameters in either sex were observed, and there were no noteworthy organ weight changes (see Tables B-4 and B-5). Microconcretions in renal tubules were observed in 3/15, 7/10, and 7/10 females in the low-, mid-, and high-dose groups, respectively (see Table B-6). The severity of these lesions was minimal in all dose groups. Incidences in the control group were not reported in the data table provided in the study summary, but the conclusion text stated that microconcretions were absent in the control animals. Focal interstitial nephritis occurred in 2/10 high-dose females, and single incidences of focal lymphoid infiltration and chronic nephritis were observed in low-dose females. A single incidence of focal interstitial nephritis was observed in high-dose males. Similar to control animals and those dosed with Kasal™, several animals in the Levair® groups also exhibited signs of chronic pneumonia and tracheitis, unrelated to treatment.

This study is considered by the U.S. EPA to be unsuitable as a basis for quantitative evaluation due to availability only as a limited summary from a secondary source and poor reliability of the performing laboratory (IBT). Tentative effect levels are identified here for comparative purposes only. A tentative LOAEL of 210.09 mg/kg-day (lowest dose tested) was determined for female rats based on the dose-related increase of microconcretions in the renal tubules. A NOAEL could not be determined for female rats. For male rats, a tentative NOAEL of 1,909.53 mg/kg-day was determined based on the lack of toxicologically relevant treatment-related effects following dietary exposure to Levair® for 90 days.

Levn Lite®

Doses of Levn Lite® were reported as 0, 155.36, 545.64, and 1,796.95 mg/kg-day for male rats and 0, 181.18, 701.65, and 2,070.10 mg/kg-day for female rats [Anonymous (1972) as cited in [ECHA \(1972c\)](#)]. Three animals (sex and dose group not reported) treated with Levn Lite® died. Similar to the mortalities in the Levair® groups, the deaths were attributed to trauma incurred during collection of blood samples. It was reported that no unexpected behavioral reactions occurred. Weekly body weight and food consumption data were not reported, but the 90-day average total weight gains and total food consumption were reported (see Table B-7). Total body-weight gain of treated male rats was higher than controls by 17, 5, and 5% in the low-, mid-, and high-dose groups, respectively. Low-dose males exhibited similar food consumption rates compared to controls, while slight decreases (<10%) were seen in the mid- and high-dose groups. Unlike the male rats, total body-weight gain was decreased in female rats compared to the control group by 10, 13, and 18% in the low-, mid-, and high-dose groups, respectively. This was accompanied by slight decreases in food consumption compared to the control group of 8, 8, and 1%, respectively. Although final body weights were not reported, the study summary noted that no statistical differences were found between treated and control rats based on final body weights or total weight gains for either sex.

The available ECHA summary reported that no treatment-related effects were observed based on hematology, clinical chemistry, urinalysis, organ weights, or gross pathological findings in rats dosed with Levn Lite®. Mean values of these data without measures of variance or statistical analysis were provided in the summary. Independent review of the magnitudes of change show similar increases in neutrophil (24%), monocyte (24%), and eosinophil (100%) counts in high-dose male rats as those observed for males treated with Kasal™ and Levair® (see Table B-3). Eosinophil levels in females were decreased 78%, compared with controls; all other changes in females were <10% in magnitude. The largest serum chemistry changes were a 19% increase and a 25% decrease in serum ALT in high-dose male and female rats, respectively,

compared with controls (see Table B-4). Compared to controls, relative kidney-to-body weight in female rats was statistically significantly increased in high-dose females by 10% (see Table B-5). In addition, relative kidney-to-brain weight was increased by 9% and absolute kidney weight was increased by 5% in this group, compared to controls. Statistically significant weight changes in other organs included a 14% increase in relative testes-to-body weight and a 9% decrease in brain-to-body weight measures in low-dose male rats, compared with controls, and a 7% decrease in absolute brain weight in mid-dose females. Similar to females treated with Kasal™ and Levair®, there was a dose-related increase in the incidences of microconcretions in renal tubules in female rats, but not males, treated with Levn Lite® (see Table B-6). The incidences were 4/15, 5/10, and 9/10 in the low-, mid-, and high-dose groups, respectively. The severity of these lesions was minimal in the low- and high-dose females and mild in the mid-dose females. Incidences in the control group were not reported in the data table provided in the study summary, but the conclusion text stated that microconcretions were absent in the control animals. Incidence of kidney focal lymphoid infiltration (5/10) in the mid-dose group was also significant. There was one case of hydronephrosis at the low dose. Non-neoplastic findings in other organs did not appear to be related to treatment.

This study is considered by the U.S. EPA to be unsuitable as a basis for quantitative evaluation due to availability only as a limited summary from a secondary source and poor reliability of the performing laboratory (IBT). Tentative effect levels are identified here for comparative purposes only. A tentative LOAEL of 181.18 mg Levn Lite®/kg-day (lowest dose tested) was determined for female rats based on the dose-related increase of microconcretions in the renal tubules. A NOAEL could not be determined for female rats. For male rats, a tentative NOAEL of 1,796.95 mg/kg-day was determined based on the lack of toxicologically relevant treatment-related effects following dietary exposure to Levn Lite® for 90 days.

[FDA \(1975\)](#) reported that, in 1973 and 1974, IBT conducted 90-day feeding studies in female rats with Kasal™, Levair®, and Levn Lite® in follow-up to the 90-day feeding studies conducted in 1972 (described in above). These follow-up tests apparently evaluated exposures at lower dose levels than the previous studies, but focused primarily on assessing changes in body and kidney weights. [FDA \(1975\)](#) reported that female rats fed diets containing 300 and 1,000 ppm Kasal™ and Levair® for 90 days exhibited a higher incidence of microconcretions in renal tubules when compared with controls. These studies were not available. A summary of the study conducted using Levn Lite® was available in ECHA [Anonymous (1973) as cited in [ECHA \(1973\)](#)], although the ECHA summary indicated that histopathology was not evaluated. Female albino rats (15/group; strain not specified) were fed diets containing 0 (plain diet), 300, or 1,000 ppm Levn Lite® ad libitum for 90 days. Animals were monitored daily for abnormal reactions and mortality. Rats were weighed on the first day of the test and monthly thereafter. The study summary indicated that food consumption was not monitored. Rats surviving to the end of the 90-day exposure period were sacrificed and examined grossly. Kidneys were removed and weighed. Statistical analysis was conducted on absolute and relative kidney weights as ANOVA followed by a Student's *t*-test. Five deaths not attributed to treatment were reported to have occurred during the study. No abnormal behaviors were observed. There were no significant differences between treated rats and control rats in final body weights, body-weight gains, kidney weights, or gross pathological observations. Although not statistically significant, absolute kidney weights were reduced by 23 and 24% compared to controls in the 300 and 1,000 ppm groups, respectively. Relative kidney weights of treated rats in both dose groups were reduced by 6% from controls. These magnitude changes were larger than seen in the previously

described 90-day rat study for Levn Lite®. The ECHA summary indicated that histopathology was not examined, so it is not clear if these changes in kidney weights were accompanied by microscopic changes.

[FDA \(1975\)](#) also reported that IBT conducted separate histologic evaluations of the kidney tissues of both rats and dogs fed Kasal™, Levair®, or Levn Lite®, but these reports are not available. [FDA \(1975\)](#) did not describe the pathology results in any detail but noted that microconcretions were not observed in dogs fed Kasal™, which contradicts the findings of microconcretions in renal tubules observed in the 90-day dog study summarized below.

Industrial Bio-Test Laboratories, Inc. 90-Day Feeding Study in Dogs

The 90-day dog study predated (1972) established OECD guidelines and GLP [Anonymous (1972) studies as cited in [ECHA \(1972a, 1972d\)](#)]. Beagle dogs (4/sex/dose), age unknown, were fed diets ad libitum containing 0 (plain diet), 0.3, 1.0, or 3% Kasal™ (basic SALP) or Levn Lite® (acidic SALP) for 90 days. Daily intake doses (as noted below) of each commercial product were reported in the individual study summaries, calculated using the mean of the weekly body weight and food consumption data (excluding the 5th week from the mid-dose female group due to illegible figures in the report). Animals were monitored daily for mortality and clinical signs of toxicity. Body weights were recorded prior to study initiation and weekly thereafter. Food consumption was calculated weekly. Blood and urine were collected at the beginning of the study and on Study Days 42 and 84 for hematological (total and differential leucocyte counts, erythrocyte counts, hemoglobin, and hematocrit) and clinical chemistry (BUN, glucose, ALP, ALT, and aspartate aminotransferase [AST]) measurements, and for urinalysis. At sacrifice, all major tissues and organs were examined grossly. Liver, kidneys, heart, brain, spleen, gonads, adrenal glands, thyroid gland, and pituitary organs were weighed. Histological analysis was performed on an unreported number of tissues (based on the results that were presented in the study summary, examined tissues at least included kidneys, liver, lungs, prostate, spleen, heart, uterus, ovaries, pancreas, mesenteric lymph node, gonads, and spinal cord). Body weight, food consumption, and limited histological findings on select tissues were the only quantitative data provided in the available summaries; measures of variance and details on statistical analysis were not provided in the study summaries.

Kasal™

Daily intakes were reported to be equivalent to 0, 94.23, 322.88, and 1,107.12 mg/kg-day for male dogs and 0, 129.31, 492.77, and 1,433.56 mg/kg-day for female dogs fed diets containing Kasal™ for 90 days [Anonymous (1972) as cited in [ECHA \(1972a\)](#)]. All dogs treated with Kasal™ survived until the end of the study, and no clinical signs related to treatment were reported. Quantitative data tables of mean body weight at week 0, overall weight gain, and mean food consumed weekly without measures of variance were available for independent review. No treatment-related effects on body weight or food consumption were found.

Hematological, clinical chemistry, and urine endpoints were reported to be unaffected by treatment, although the data were not provided. Similarly, no quantitative organ weight data were provided; the study summary reported that no effects were observed. Gross pathology findings were described as those attributed to spontaneous disease. Based on histopathological examinations, the animals (including controls) appeared to be in poor general health. Chronic interstitial pneumonia was observed in at least two male and female animals in every treatment group, including controls; liver congestion was also observed in every group. One low-dose

female and one mid-dose female had bronchopneumonia. Histological data were selectively reported in tabular format. The study summary indicated that all tissues and organs not mentioned in the tables were histologically normal. Incidences of tubular concretions of moderate severity were reported in 2/4 males and 1/4 females fed the high-dose diet (see Table B-8). These concretions were described as unusually large and more numerous than those typically observed in untreated dogs. The conclusion section of the study summary noted that a few other calcified microconcretions present in the lumen of renal tubules located at the corticomedullary junction and/or medulla of the kidney were attributed to normally occurring disease. One low-dose male and one high-dose male also presented minimal or slight focal lymphoid infiltration. Findings in other organs were unremarkable.

This study is considered by the U.S. EPA to be unsuitable as a basis for quantitative evaluation due to availability only as a limited summary from a secondary source and poor reliability of the performing laboratory (IBT). Tentative effect levels are identified here for comparative purposes only. The highest dose tested was identified as the tentative LOAEL (1,107.12 mg Kasal™/kg-day for males and 1,433.56 mg Kasal™/kg-day for females) based on the occurrence of microconcretions of moderate severity in the renal tubules of male and female dogs. The mid-dose was tentatively identified as the NOAEL (322.88 mg Kasal™/kg-day for males and 492.77 mg Kasal™/kg-day for females).

Levn Lite®

Daily intakes were reported to be equivalent to 0, 94.55, 345.21, and 1,038.77 mg/kg-day for male dogs and 0, 118.66, 511.06, and 1,460.76 mg/kg-day for female dogs fed diets containing Levn Lite® for 90 days [Anonymous (1972) as cited in [ECHA \(1972d\)](#)]. There were no deaths reported in dogs dosed with Levn Lite®. No clinical signs related to treatment were described. Like Kasal™, body weight and food consumption data were presented as means in the absence of measures of variance, and no statistical analyses were provided in the study summary. No treatment-related effects on body weight or food consumption were found.

Hematological, clinical chemistry, urinalysis, and organ weight data were not available for independent review, but it was reported that no effects were observed for any of these endpoints. Gross pathology findings were attributed to spontaneous disease. Consistent with observations in controls, chronic interstitial pneumonia and congestion in the liver were identified in animals from all dose groups. No renal tubular concretions were observed in dogs treated with Levn Lite® (see Table B-8). The only observed effect in the kidney was minimal to slight congestion in a single mid-dose male. Findings in other organs were unremarkable.

This study is considered by the U.S. EPA to be unsuitable as a basis for quantitative evaluation due to availability only as a limited summary from a secondary source and poor reliability of the performing laboratory (IBT). Tentative effect levels are identified here for comparative purposes only. Tentative NOAEL values of 1,038.77 and 1,460.76 mg/kg-day for males and females, respectively (the highest dose), were determined based on the lack of treatment-related effects in beagle dogs administered Levn Lite® in the diet for 90 days.

Katz et al. (1984)

In a GLP-compliant, OECD 422 guideline study, beagle dogs (6/sex/group), approximately 7–9 months of age, were exposed to daily diets containing 0, 0.3, 1.0, or 3.0% Levair® in corn oil vehicle (1% w/w) for 6 months ([Katz et al., 1984](#)). These diets were

equivalent to reported mean intakes of 0, 118, 317, and 1,034 mg/kg-day of acidic SALP in males and 0, 112, 361, and 1,087 mg/kg-day in females, based on body weight and food consumption data. The basal diet was analyzed for appropriate nutrients and contaminants, but results were not reported. Throughout the study, animals were observed twice daily for mortality and clinical signs. Body weights were recorded weekly, and food consumption was recorded daily. Animals were subjected to ophthalmological examinations both prior to study initiation and at termination. Hematology, clinical chemistry, and urinalysis were described as being done in accordance with the [U.S. EPA \(1978\)](#) standards. Prothrombin, activated partial thromboplastin times, and serum levels of inorganic phosphorus were also measured. At 2-month intervals, fecal samples were tested for occult blood. At necropsy, heart, liver, kidneys, gonads, prostate, pituitary, thyroid, adrenals, and brain weights were recorded. Microscopic analysis was performed on these and 25 additional tissues (not specified), and on any significant gross lesions. Data were analyzed by one-way ANOVA and Dunnett's *t*-tests. Data were considered significant at $p < 0.05$.

No mortalities were reported. Clinical signs were described as not related to treatment. Food consumption was reduced throughout much of the study in the treated dogs, significantly so in females at various times, but not necessarily in relation to dose (see Table B-9). It was reported that mean body weights of all groups, presumably including controls, increased 5–18% over the course of the study and that reductions in body weights observed in all groups at the end of the study (Week 27) were due to pretermination tests and increased handling. No statistically significant differences in mean body weights were found between male or female test groups and their respective controls at any time during the study (data not shown). The report indicated that no toxicologically relevant changes in ocular, hematological, or clinical chemistry endpoints were observed and that all values remained within the expected range for animals of this age and strain (data not shown). There were no urinalysis changes, abnormal fecal occult blood results, or significant organ weight changes in treated groups, compared with controls (data not shown). No abnormal gross or microscopic changes were reported (data not shown). None of these data other than food consumption were available for independent review.

NOAELs of 1,034 and 1,087 mg Levair®/kg-day for males and females, respectively (the highest dose), are determined based on the lack of treatment-related effects in beagle dogs administered Levair® in the diet for 6 months.

[Pettersen et al. \(1990\)](#); [Anonymous \(1987\)](#) as cited in [ECHA \(1987\)](#)

The toxicity of Kasal™ in beagle dogs following dietary exposure for 26 weeks was investigated by [Pettersen et al. \(1990\)](#). Additional study details that were not available in the published report were presented in a study summary in ECHA [[Anonymous \(1987\)](#) as cited in [ECHA \(1987\)](#)]. Groups of beagle dogs (4/sex/dose) were fed diets containing nominal concentrations of 0, 3,000, 10,000, or 30,000 ppm Kasal™ in 0.5% w/w corn oil for 26 weeks. Measured Kasal™ consumption was 0, 112, 390, or 1,143 mg/kg-day for males and 0, 106, 323, or 1,251 mg/kg-day for females. Diet was analyzed for aluminum content (3–4, 10, 22–27, and 75–80 mg/kg-day in the control, low-, mid- and high-dose groups, respectively), but not for phosphate or calcium. Animals were observed at least twice daily for clinical signs of toxicity and mortality. Food consumption was recorded 2–3 times/week and body weights were determined weekly. Ophthalmoscopic examinations were done prior to study initiation and at termination. Urine and fecal samples were collected overnight using metabolism cages prior to study initiation and at termination. Fasting blood samples were collected from all animals prior

to initiation and at sacrifice for hematological (hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, and platelet count) and clinical chemistry (BUN, creatinine, sodium, potassium, chloride, phosphorus, ALT, AST, ALP, γ -glutamyl transferase [GGT], sorbitol dehydrogenase [SDH], total bilirubin, total protein, albumin, globulin, glucose, calcium, cholesterol, and triglyceride) analysis. Heart, liver, kidneys, ovaries, testes, thyroid, adrenals, and brain were weighed at necropsy. More than 35 tissues were fixed for microscopic examination. Aluminum concentrations in trabecular bone and brain samples were determined using an atomic absorption spectrophotometer. Body weights, food consumption, clinical laboratory test values, and tissue aluminum concentration data were analyzed by one-way ANOVA followed by appropriate post-hoc tests, including the Neuman-Keuls test. Data were considered significant at $p < 0.05$.

Data available for independent review were limited to the aluminum concentrations measured in bone and brain ([Pettersen et al., 1990](#)); the remaining results were reported in text only (including the ECHA summary). No mortalities were observed. Clinical signs were not discussed in the published paper, but ECHA reported erythema of the gums in one male and two females in both the low- and mid-dose groups. A sharp, transient, statistically significant decrease in food consumption during Study Week 24 was reported in male dogs at 1,143 mg/kg-day (presumably reflecting an unexplained problem with the food, health, or handling of the animals in that group at that time), leading to a precipitous decrease in body weights during Weeks 24–25 in that group (data not shown). The published report stated that there was no effect on food intake or body weight in females. Additional information provided in ECHA were terminal body weights of 85, 89, and 81% of controls in males and 93, 94, and 83% of controls in females in the low-, mid-, and high-dose groups, respectively, with the body weights in high-dose females consistently lower than controls throughout the study. This information is difficult to interpret, however, in the absence of data on body weights at study initiation and body-weight gains during the study. The published paper reported that there were no treatment-related effects on hematology, serum chemistry, or urinalysis endpoints, without presenting any data. The ECHA summary reported some sporadic serum chemistry changes, including a 22% decrease in serum creatine and a 3% decrease in sodium in high-dose males at termination, and a 5% decrease in serum calcium and 25% decrease in phosphorus at 14 weeks in females at 323 and 1,251 mg/kg-day, respectively.

The only organ weight change reported in the published paper was a decrease in testes weight in high-dose males. The ECHA summary reported this as a statistically significant 31% decrease in absolute testes weight, with no change in relative testes weight and suggested that the decrease in absolute testes weight reflected the reduction in body weight observed in this group. ECHA also reported that relative kidney weights were significantly increased (magnitude not reported) in this group but that absolute kidney weights did not differ significantly from controls. This, too, may reflect the decrease in body weight in this group. No organ weight changes were observed in females. Pathology observations indicated that 2/4 high-dose males had reduced testes sizes compared to controls, with moderate seminiferous tubule germinal epithelial cell degeneration and atrophy, consistent with the decreases in absolute testes and body weight in this group. Other pathology findings in high-dose males were mild to moderate hepatocyte vacuolation and hypertrophy and mild bile stasis with bile canaliculi (3/4 males) in the liver and very mild (2/4) to mild (2/4) tubular-glomerulonephritis in the kidney. It is unclear to what extent the liver and kidney findings may reflect the abrupt decrease in body weight at Week 24 in this group. There were no reported findings in low- or mid-dose males. Tubular-glomerulonephritis

was observed in 1/4 control males. Necropsy results and microscopic findings in females were not described in the study report, but the ECHA summary noted that treated females did not exhibit any significant treatment-related pathological changes. Trabecular bone concentrations of aluminum did not differ significantly from controls in males or females at any dose. Brain aluminum concentrations were significantly increased (~60%) only in high-dose females.

Observations in high-dose males included precipitous decreases in food consumption and body weight near the end of the study, presumably reflecting an unexplained problem with the food, health, or handling of the animals in that group at that time. Decreased group mean absolute testes weight and testicular atrophy in 2/4 dogs from this group likely reflect the abrupt decrease in body weight, as does an observed increase in relative kidney weight. Mild liver (hepatocyte vacuolation and hypertrophy) and kidney (tubular-glomerulonephritis) lesions in this group may or may not have been secondary to the plunge in body weight. The researchers reported no effects in the low- or mid-dose males or in female dogs at any dose. These results suggest that for male dogs, the mid dose of 390 mg/kg-day is a clear NOAEL for Kasal™ administered continuously in the diet for 26 weeks. It is less clear how to interpret findings in males at the high dose, but for this assessment, the high dose of 1,143 mg/kg-day is tentatively considered a LOAEL based on mild liver and kidney effects. For females, the high dose of 1,251 mg/kg-day is a NOAEL.

Reproductive/Developmental Studies

Anonymous (2002a) as cited in [ECHA \(2002d, 2002e\)](#)

An unpublished, GLP-compliant, OECD guideline 422 repeated-dose toxicity study with a reproductive/developmental screening test that is summarized in ECHA [Anonymous (2002) as cited in [ECHA \(2002d\)](#)] evaluated the effects of orally administered triphosphoric acid aluminum salt (1:1) (tradename K-Fresh 100P) in rats. Commercially available Crj:CD(SD)IGS rats (10/sex/dose) were dosed with 0 (vehicle), 100, 300, or 1,000 mg/kg-day triphosphoric acid aluminum salt (94.7% pure) dissolved in 0.5% carmellose sodium in purified water (vehicle) via gavage. Males were dosed for 46 days, beginning 14 days prior to mating. Females were dosed from 14 days prior to mating, then throughout mating, gestation, delivery, and up to postnatal day (PND) 4. Doses were selected based on a 14-day preliminary study in rats that reported no observed effects at the highest dose of 1,000 mg/kg-day. Exposure doses were prepared weekly and were analytically verified by comparing absorbance to standard solutions. Animals were observed 4 times daily for mortality, external appearance, and behavior. Detailed clinical observations were not made. Body weights were measured prior to study initiation and on Days 1, 2, 5, 7, 10, and 14, and weekly thereafter. Food consumption was monitored daily, and water consumption was evaluated on Days 43–44 of administration. Blood was collected (5/sex/dose) on the day following the last dosing for hematological and clinical chemistry measurements. Urine was collected on Days 43–44 for urinalysis (males only). The study did not include neurobehavioral analysis. At sacrifice, all parental animals were subject to macroscopic examination and reproductive organs were weighed. Gross and histological analysis was performed on >40 tissues from animals in all dosing groups, with special attention to reproductive organs, and on any gross findings.

Sperm parameters were not included in the study. Female estrous cyclicity was monitored 10 days prior to dosing through copulation. Reproductive parameters (copulation, corpora lutea, implantation sites/indices, gestation, delivery) were monitored. Litter examinations included the number of surviving offspring, viability through PND 4, sex, external appearance, body weights

(at birth, and on PNDs 1 and 4), and body-weight gain. Offspring were sacrificed on PND 4, and pups were grossly examined. Bartlett's test was used for statistical analysis of body weight/body-weight gain, growth rate, feed consumption, urinalysis, hematology and clinical chemistry, and organ weights, and for reproductive and developmental parameters. ANOVA was applied in cases of equal variance, followed by Dunnett's test. The Kruskal-Wallis test was applied for data sets of unequal variance; when no significance was found, a Mann-Whitney U-test was applied. The litter was used as the experimental unit for determination of the live birth index, sex ratio, viability index, and pup body weights. Incidence data were analyzed using a multiple-sample χ^2 test followed by a two-sample χ^2 test. When mismatches occurred, a Fisher's exact test was used. A value of $p < 0.05$ was considered significant. Minimal quantitative data were provided in the summary available for review.

All parental animals survived to the end of the study. Clinical signs were limited to a swollen abdomen and soiling of perioral fur in one high-dose male on the day of autopsy and a subcutaneous mass first observed on gestation day (GD) 13 in one female from the 300 mg/kg-day group. Body weights and body-weight gains in treated males and females were comparable to controls (data not provided). A reduction in food consumption observed in males was transient and not dose-related. Food consumption in treated females was comparable to controls. Mean corpuscular volume was significantly low in females at 1,000 mg/kg-day. There were no other hematological changes in females, and no significant hematological effects in males. High-dose females exhibited significantly reduced levels of total protein and calcium, compared with controls, but the magnitudes of the reported decreases were not reported, and the data were not shown. Calcium was also significantly reduced in females at 100 mg/kg-day, but not at 300 mg/kg-day. At 1,000 mg/kg-day, a decrease in urine pH was observed in males, and was attributed to the low pH of the test material. Absolute and relative spleen weights were reported to be significantly reduced, compared with controls, in females in the 100 and 1,000 mg/kg-day groups (magnitudes not reported and data not shown); no differences were observed in the 300 mg/kg-day group. No significant organ weight changes were reported in males. At necropsy, several individual macroscopic findings were reported across dose groups, but incidences were low, sporadic, and not statistically significant. Deformity of the liver with multi-focal yellowish-white spots was observed in one low-dose male, and atrophy of the bilateral testes and epididymides was observed in one mid-dose male and one high-dose male; this high-dose male failed to establish a pregnancy in a paired female. There were no dose-related or significant macroscopic changes in females. Histopathological lesions were also low in incidence and sporadic. Histological examinations identified severe atrophy of the testes with decreased sperm in one high-dose male that did not establish a pregnancy in a paired female. Atrophy of the testes was also observed in two control and four mid-dose males, but with lesser severity. In another high-dose male that failed to establish pregnancy in a paired female, mild myocardial degeneration was observed. Single incidences of dilated cerebral ventricles and extramedullary hematopoiesis in the spleen were observed in females at 1,000 and 300 mg/kg-day, respectively. Localized necrosis of the liver and atrophy of the thymus were described as being sporadic in females at 1,000 mg/kg-day. One female that did not become pregnant had vaginal closure/inflammation in the uterus horn.

The estrous cycles in females were not affected by treatment. Copulation, gestation, and nursing indices were comparable across groups. One mid-dose female that did not give birth by GD 25 had two dead and five live fetuses when sacrificed, and another mid-dose female delivered seven dead fetuses. The gestation index at 300 mg/kg-day was 90%, compared to

100% in all other groups. The gestation index decrease did not display a relationship to dose. As surviving fetuses were present in the uterus and no comparable effect was observed in the higher dose group, this effect is not considered as adverse but rather incidental. The fertility index of the high-dose group was decreased (significance not specified) due to infertility in 1/10 males with severe testes atrophy and 1/10 females with vaginal closure and inflammation of the uterine horn. Pregnancy rates, however, were reported to fall within the range of historical data. There were no dose-related changes in corpora lutea, number of implantations, implantation and delivery indices, or total number of offspring.

Limited data on offspring parameters were provided. No toxicologically relevant effects in offspring were described. The live birth, survival, and viability indices were reported to be comparable across all groups. The few neonatal deaths noted occurred with equal incidence to controls. There were no notable clinical signs, body weight or body-weight changes, or gross findings in offspring.

A maternal and reproductive/developmental NOAEL of 1,000 mg/kg-day (the highest dose tested) is identified; a LOAEL could not be determined.

2.2.2. Inhalation Exposures

No studies of animals exposed to aluminum phosphate salts by inhalation have been identified in the literature searches or secondary sources reviewed.

2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4 provides an overview of genotoxicity studies of aluminum phosphate salts.

Table 4. Summary of Genotoxicity Data for Aluminum Phosphates

Endpoint Test Substance	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation Aluminum dihydrogen tripolyphosphate	<i>Salmonella</i> <i>typhimurium</i> TA1535, TA1537, TA98, TA100	0, 313, 625, 1,250, 2,500, 5,000 µg/plate	–	–	Preincubation assay. No evidence of mutagenicity in any of the strains tested, with or without rat liver S9 activation. Precipitation occurred at ≥1,250 µg/plate without S9 and ≥625 µg/plate with S9. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2002) as cited in ECHA (2002b)
Mutation Aluminum orthophosphate	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	0, 50, 150, 500, 1,500, 5,000 µg/plate	–	–	Preincubation assay. No evidence of mutagenicity with or without rat liver S9 activation. Precipitation was observed at 5,000 µg/plate without metabolic activation. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2010) as cited in ECHA (2010e)
Mutation Aluminum metaphosphate	<i>S. typhimurium</i> TA1535, TA1537, TA98, TA100	0, 313, 625, 1,250, 2,500, 5,000 µg/plate	–	–	In both preincubation and plate incorporation assays, there was no evidence of mutagenicity with or without rat liver S9 activation. Slight precipitation at all concentrations. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2015) as cited in ECHA (2015b)

Table 4. Summary of Genotoxicity Data for Aluminum Phosphates

Endpoint Test Substance	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
Mutation Aluminum dihydrogen tripolyphosphate	<i>Escherichia coli</i> WP2 uvrA pKM 101	0, 313, 625, 1,250, 2,500, 5,000 µg/plate	–	–	Preincubation assay. No evidence of mutagenicity with or without rat liver S9 activation. Precipitation occurred at ≥1,250 µg/plate without S9 and ≥625 µg/plate with S9. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2002) as cited in ECHA (2002b)
Mutation Aluminum orthophosphate	<i>E. coli</i> WP2 uvrA	0, 50, 150, 500, 1,500, 5,000 µg/plate	–	–	Preincubation assay. No evidence of mutagenicity with or without rat liver S9 activation. Precipitation was observed at 5,000 µg/plate without metabolic activation. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2010) as cited in ECHA (2010c)
Mutation Aluminum metaphosphate	<i>E. coli</i> WP2 uvrA	0, 313, 625, 1,250, 2,500, 5,000 µg/plate	–	–	In both preincubation and plate incorporation assays, there was no evidence of mutagenicity with or without rat liver S9 activation. Slight precipitation occurred at all concentrations. No cytotoxicity was observed; tests were done to recommended limit concentrations. The positive controls gave expected results.	Anonymous (2015) as cited in ECHA (2015b)
DNA repair (rec assay) Aluminum phosphate	<i>Bacillus subtilis</i> H17 (Rec ⁺ , arg ⁻ , try ⁻) and M45 (Rec ⁻ , arg ⁻ , try ⁻)	0.05 mL of 0.005–0.5 M	–	NA	No evidence of recombination repair function in plates exposed for 24 h at 4°C and then at 37°C overnight.	Kanematsu et al. (1980)

Table 4. Summary of Genotoxicity Data for Aluminum Phosphates

Endpoint Test Substance	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
Genotoxicity studies in mammalian cells—in vitro						
Mutation Aluminum orthophosphate	Mouse lymphoma L5178Y cells	0, and six concentrations ranging from 20 to 320 µg/mL	–	–	The test material did not induce statistically significant increases in mutant frequency after incubation for 4 h with rat liver S9 activation or after 24 h without metabolic activation. Precipitation occurred at ≥20 µg/mL. No cytotoxicity was observed. The positive controls gave expected results.	Anonymous (2010) as cited in ECHA (2010g)
Mutation Aluminum metaphosphate	Mouse lymphoma L5178Y cells	0.00032, 0.0016, 0.008, 0.04, 0.2, 1, 5 mg/mL	–	–	No significant increases in mutation frequencies after 3- or 4-h incubations with test material either with or without metabolic activation. Slight precipitation occurred at all concentrations tested. No cytotoxicity reported. The positive controls gave expected results.	Anonymous (2015) as cited in ECHA (2015a)
CA Aluminum dihydrogen tripolyphosphate	Chinese hamster CHL/IU cells	Without metabolic activation: 0, 6.25, 12.5, 25, 50, 100 µg/mL With metabolic activation: 0, 250, 500, 1,000, 1,500, 2,000 µg/mL 0, 1,600, 1,800, and 2,000 µg/mL with metabolic activation (confirmation study)	–	+/-	No increases in cells with structural or numerical CAs following treatment for 6 h in absence of metabolic activation. With activation, increased incidences of cells with structural, but not numerical, aberrations were observed at 2,000 µg/mL. However, dose-related increases in cytotoxicity were reported at ≥50 µg/mL without metabolic activation and ≥1,000 µg/mL with metabolic activation along with a decrease in pH. The positive controls gave expected results.	Anonymous (2002) as cited in ECHA (2002c)

Table 4. Summary of Genotoxicity Data for Aluminum Phosphates

Endpoint Test Substance	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
CA Aluminum orthophosphate	Primary human lymphocytes	0, 20, 40, 80, 160, 320, 480 µg/mL	–	–	Negative for CAs following exposure for 4 h with and without S9 metabolic activation or for 24 h without S9 activation. Precipitation occurred at ≥20 µg/mL at the end of the 4-h exposure and at ≥320 µg/mL at harvest. In the 24-h exposure group, precipitation occurred at ≥40 µg/mL. The positive controls gave expected results.	Anonymous (2010) as cited in ECHA (2010f)
MN Aluminum metaphosphate	Primary human peripheral lymphocytes	0, 0.3162, 1.0, 3.162, 10.0 µg/mL	–	–	No increases in the frequency of cells with MN with or without metabolic activation following 4- or 24-h exposures. Precipitation occurred at 10.0 µg/mL with and without metabolic activation. No cytotoxicity was observed. The positive controls gave expected results.	Anonymous (2016) as cited in ECHA (2016)

^a+ = positive; ± = weakly positive; – = negative; +/- = equivocal.

CA = chromosomal aberration; DNA = deoxyribonucleic acid; MN = micronuclei.

2.3.1. Genotoxicity

The genotoxicity of aluminum phosphate has been evaluated in a limited number of in vitro studies (see Table 4 for more details). Data indicate that in bacteria, the aluminum phosphate compounds, aluminum dihydrogen triphosphate, aluminum orthophosphate, and aluminum metaphosphate, are not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA98, or TA100 or in *Escherichia coli* WP2 uvrA, either in the presence or absence of activation [Anonymous (2015) as cited in [ECHA \(2015b\)](#); Anonymous (2010) as cited in [ECHA \(2010c\)](#); Anonymous (2010) as cited in [ECHA \(2010e\)](#); Anonymous (2002) as cited in [ECHA \(2002b\)](#)]. There were also no mutations observed in mouse lymphoma cells under any of the conditions tested [Anonymous (2015) as cited in [ECHA \(2015a\)](#); Anonymous (2010) as cited in [ECHA \(2010g\)](#)]. Aluminum phosphates did not induce clastogenic effects in vitro. No increases in the frequency of chromosomal aberrations (CAs) in Chinese hamster CHL/IU cells or in human lymphocytes with or without metabolic activation [Anonymous (2010) as cited in [ECHA \(2010f\)](#); Anonymous (2002) as cited in [ECHA \(2002c\)](#)], and no increases in micronuclei (MN) in human peripheral lymphocytes, were observed [Anonymous (2016) as cited in [ECHA \(2016\)](#)]. Finally, in *Bacillus subtilis*, there was no evidence of deoxyribonucleic acid (DNA) repair following exposure to aluminum phosphate ([Kanematsu et al., 1980](#)).

2.3.2. Other Animal Studies

[Schaeffer et al. \(1928\)](#) fed groups of 40 mice (20/sex; strain not specified) bread with aluminum phosphate (2.07 g of aluminum for 1,000 g of bread; type of phosphate not specified) or bread of similar composition but raised with alum baking powder (4.1 g of aluminum for 1,000 g of bread) for 4 months. At the end of the 4-month exposure, the mice from both groups exhibited paracellular necrosis of the superficial epithelium of the stomach and of the tops of certain intestinal villi. None of the mice fed bread leavened with yeast demonstrated this lesion. The mice evaluated in this study were coupled and allowed to reproduce. The groups of mice fed bread leavened with aluminum phosphate or alum baking powder produced fewer offspring (193 and 71, respectively) than mice fed bread with yeast (300 offspring). In a follow-up experiment by the same researchers, four groups of 10 couples of mice were fed bread with yeast plus 4% physiological saline mixture, bread with yeast plus 13% saline mixture, bread with alum-phosphate baking powder (4.4% of aluminum) plus 4% saline mixture, or bread with alum-phosphate baking powder (1.3%) for 4 months. Mice fed the bread containing 4.4% aluminum as alum-phosphate baking powder experienced increased mortality of offspring during the first week of life (23% mortality rate compared to 10% mortality rate in mice fed bread without alum-phosphate baking powder) and decreased number of offspring. The ovaries of these animals contained a large number of atretic follicles and were greatly reduced in size.

Aluminum phosphate salts exhibit low acute lethal potential based on unpublished data in secondary sources. The oral median lethal dose (LD₅₀) values determined in rats were >2,000 mg/kg for aluminum orthophosphate, aluminum dihydrogen triphosphate, and triphosphoric acid aluminum salt (1:1); no clinical signs or body-weight changes were noted [Anonymous (2013) as cited in [ECHA \(2013\)](#); Anonymous (2012) as cited in [ECHA \(2012a\)](#); Anonymous (2010) as cited in [ECHA \(2010a\)](#); Anonymous (2002) as cited in [ECHA \(2002a\)](#)]. In a review, [Weiner et al. \(2001\)](#) reported the following oral LD₅₀ values for rats: >1,000 mg/kg for monoaluminum phosphate (MALP), >4,640 mg/kg for aluminum metaphosphate (ALMP), and 5,580 mg/kg for SALP, as well as a dermal LD₅₀ of >4,640 mg/kg for both MALP and ALMP, citing unpublished studies by Stauffer and Solutia.

Acute inhalation toxicity data for several aluminum phosphate compounds were summarized in ECHA. An inhalation median lethal concentration (LC₅₀) of >5.1 mg/L was reported for Wistar rats exposed to a monobasic aluminum phosphate (compound reported as FFB716) in powder form, nose-only for 4 hours. Although all animals in this study survived exposure, principal clinical signs observed during the first 11 days of recovery included hunched posture, ruffled fur, labored breathing, breathing noises, and salivation. Transient body-weight loss was also noted in all animals during the first day following exposure; normal body weight development was observed after test Day 4. No significant necropsy findings were reported. Similar inhalation studies on aluminum dihydrogen triphosphate and ALMP reported LC₅₀ values of >3.46 mg/L for Wistar rats and >2.17 mg/L for Sprague Dawley rats, respectively. These reported LC₅₀ concentrations represented the maximum technically achievable concentration under the conditions of the study. No mortalities were observed in either study. Rats exposed to aluminum dihydrogen triphosphate exhibited increased respiratory rate, hunched posture, and piloerection for several days following exposure, but appeared normal by Days 6 and 7 postexposure for males and females, respectively. Slight decreases in body weights were observed during the first 4 days post exposure, but normal body-weight gain was observed in all animals thereafter. No macroscopic findings were observed during necropsy.

The review by [Weiner et al. \(2001\)](#) reported that MALP and ALMP were nonirritating and slightly irritating, respectively, when applied to the skin of rabbits in 4-hour tests under occlusive conditions, citing unpublished studies by Stauffer. MALP was also reported to be mildly to moderately irritating when applied to rabbit skin for 24 hours as a 47% H₃PO₄ solution, citing the unpublished studies by Albright and Wilson. No further details were provided. Additional skin irritation results were summarized in ECHA [Anonymous (2014) as cited in [ECHA \(2014b\)](#); Anonymous (2010) as cited in [ECHA \(2010d\)](#)]. ALMP was not irritating when applied to rabbit skin under semi-occlusive conditions for 4 hours. Aluminum orthophosphate and aluminum dihydrogen triphosphate were nonirritating when applied to reconstructed human epidermis.

A broad range of eye irritation responses have been found within the class of aluminum phosphates. As reported in the review by [Weiner et al. \(2001\)](#), ALMP was found to be nonirritating in rabbits, whereas studies of MALP reported results ranging from slightly irritating to severely irritating, citing unpublished studies by Stauffer and by Albright and Wilson. Similarly, records within ECHA [Anonymous (2014) as cited in [ECHA \(2014a\)](#); Anonymous (2012) as cited in [ECHA \(2012b\)](#); Anonymous (2010) as cited in [ECHA \(2010b\)](#)] summarized eye irritation studies in rabbits that classified ALMP as nonirritating, aluminum orthophosphate as mildly irritating, aluminum dihydrogen triphosphate as irritating, and MALP as corrosive.

A study conducted by [de Chambrun et al. \(2014\)](#) performed in vivo and in vitro experiments with various aluminum compounds, including aluminum phosphate, to evaluate the potential effects of aluminum on the development or potentiation of inflammatory bowel disease. In the in vivo study, aluminum phosphate diluted in phosphate buffer saline (PBS) was administered to groups of C57BL6 mice (14 males/group) via gavage daily for 4 weeks (31 days) at a reported concentration of 1.5 mg aluminum element/kg-day, or 17.8 mg aluminum phosphate as determined for this review. No significant effects on body weights or macroscopic or microscopic changes in colonic tissues were observed in mice treated with aluminum phosphate compared with controls. However, in mice with induced colitis, aluminum phosphate

was found to increase the intensity and duration of macroscopic and histologic intestinal inflammation. Induction of inflammation was evaluated *in vitro* using human colon epithelial cell lines, HT-29 and Caco-2. Cells were incubated with 0, 10, 50, or 100 µg/mL aluminum phosphate for 3 hours. Dose-dependent increases in the expression of cytokines, IL-8 and IL1β, that were significant at 50 µg/mL suggest a pro-inflammatory effect. *In vitro*, the formation of granuloma-like cell aggregates in primary human peripheral blood mononuclear cells (PBMCs) can be used as a model to mimic early host immune responses (Je et al., 2016). To study the potential early immune responses to aluminum phosphate, PBMCs were left untreated or incubated for 4 days with increasing concentrations of aluminum phosphate (up to 100 µg/mL aluminum element). In the absence of bacteria, granuloma counts increased in a dose-related manner, and were visible at a dose as low as 5 ng of aluminum element/mL.

2.3.3. Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

Limited data on the absorption and distribution of aluminum following exposures to SALPs are available. A separate body of data evaluating the use of aluminum phosphates as adjuvants for vaccines, including toxicokinetic data following injection routes of exposure, is available (ATSDR, 2008; Baylor et al., 2002) and not reviewed here.

Absorption

Data on the absorption of aluminum phosphates are primarily limited to studies testing the effects of aluminum chemical forms on the bioavailability of aluminum as summarized in several reviews (Younes et al., 2018; Willhite et al., 2014; Greger, 1993). Early studies were impeded by the lack of suitable radioisotopes (Yokel et al., 2005), and to date, estimates of oral aluminum absorption have primarily been based only on levels detected either in serum or in urine, often from a single collection point, or a limited number of collection points, and without taking possible retention into account. The general consensus is that the bioavailability of oral aluminum from aluminum phosphates and their salts is low, foremost due to the insoluble nature of aluminum phosphates. In a human study, poor absorption was inferred when no increases in plasma aluminum levels were observed in a single measurement taken on the final day for six volunteers who ingested 2.2 g of aluminum phosphate in divided doses between meals for 3 days (Kaehny et al., 1977). In the same study, detection of aluminum in daily urine samples was regarded as an indication that some absorption through the gastrointestinal tract did occur, but no accurate estimates of bioavailability were made. In rodents, serum levels of aluminum in rats fed biscuits containing 1 or 2% of the leavening agent, [²⁶Al]-acidic SALP (acidic SALP) averaged 0.11 and 0.13%, respectively, with maximum concentrations measured at 4.2 and 6 hours post consumption (Yokel and Florence, 2006). In a similar study, aluminum bioavailability when [²⁶Al]-basic SALP was delivered to rats at concentrations of 1.5 and 3% in a processed cheese was ~0.1 and 0.3%, respectively; the time to maximum serum [²⁶Al] concentration (T_{max}) was 8–9 hours (Yokel et al., 2008). Some studies suggest that the chemical form (e.g., aluminum phosphate vs. aluminum citrate), pH of the gastrointestinal tract, and consumption of other foods may alter acidity or contain ligands that impact absorption (Younes et al., 2018; Greger et al., 1997; Berthon and Daydé, 1992; Daydé et al., 1990), but consistent data supporting these hypotheses are lacking (de Chambrun et al., 2014; Yokel and McNamara, 2001; Owen et al., 1994; Yokel and McNamara, 1988; Kaehny et al., 1977).

No data on absorption of aluminum phosphate salts via inhalation or dermal routes were identified.

Distribution

Since aluminum is known to accumulate in bone, [Hicks et al. \(1987\)](#) designed a study to measure aluminum concentrations in the femurs of male Sprague Dawley rats administered basic SALP in the diet for 28 days. Aluminum concentrations measured in the femurs of control rats ranged from below the level of detection to 0.3 ppm. Aluminum concentrations in rats fed diets containing basic SALP as Kasal™ or Kasal™II were not quantifiable (detectable levels that were below the limits of quantification). Thus, this study found no significant deposition of aluminum in bone of rats fed diets with either basic SALP formulation.

In beagle dogs fed Kasal™ for 26 weeks, the aluminum concentrations in trabecular bone of treated dogs were unchanged from controls [[Pettersen et al., 1990](#)]; Anonymous (1987) as cited in [ECHA \(1987\)](#)]. In female brains, but not male brains, aluminum concentrations were increased 1.6 times over controls in animals dosed with 30,000 ppm, but the levels were low (0.129 ppm). In another study in guinea pigs, animals were fed sponge cake diets containing SALP (only aluminum concentrations were reported), with or without orange juice (citrate), for 3 weeks ([Owen et al., 1994](#)). Compared with animals on control chow diets, aluminum contents in the femurs of animals eating sponge cake were significantly higher. No aluminum was detected in brain tissue, and compared to controls, aluminum levels in the kidney were only significantly increased in the group that received both sponge cake and orange juice. Less than 1% of ingested aluminum was found in the soluble fraction of the upper intestinal tract.

Metabolism

No data on the metabolism of aluminum phosphate salts have been identified.

Excretion

The primary route of elimination is expected to be through urine, with bile as a secondary, minor route ([Younes et al., 2018](#); [Yokel et al., 2008](#); [Greger et al., 1997](#); [Kaehny et al., 1977](#)).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

The database for aluminum phosphate salts (multiple CASRNs) is inadequate to support derivation of subchronic or chronic provisional oral reference values. Repeated-dose oral toxicity studies were identified for acidic and basic SALPs, including a 28-day dietary study in male Sprague Dawley rats with Kasal™ ([Hicks et al., 1987](#)), 90-day dietary studies in male and female albino rats with Kasal™, Levair®, and Levn Lite® [Anonymous (1972) studies as cited in [ECHA \(1972c, 1972e, 1972f\)](#)], 90-day dietary studies in male and female beagle dogs with Kasal™ and Levair® [Anonymous (1972) as cited in [ECHA \(1972a, 1972d\)](#)], and 6-month dietary studies in male and female beagle dogs with Levair® ([Katz et al., 1984](#)) and Kasal™ [([Pettersen et al., 1990](#)); Anonymous (1987) as cited in [ECHA \(1987\)](#)]. There is also a reproductive/developmental gavage study in Sprague Dawley rats with triphosphoric acid aluminum salt [Anonymous (2002) as cited in [ECHA \(2002d\)](#)]. No repeated-dose oral toxicity studies were identified for other forms of aluminum phosphate salts.

Limitations of these studies are significant. Several of the studies are available only as selectively described submissions to the ECHA database. Information in all such cases was insufficient to support independent review and evaluation of the study. In addition, the 90-day rat and dog studies [Anonymous (1972) as cited in [ECHA \(1972c, 1972e, 1972f\)](#)] were reported by [FDA \(1975\)](#) to have been conducted by IBT, a laboratory found by OECD to be unreliable, further lowering confidence in these results. Although the 6-month dog studies were published, few of the data are shown, again providing limited basis for independent study evaluation. None of the studies provided any information on phosphate or calcium content of the baseline diets fed to the animals. Dietary phosphate data are necessary to ensure that the total phosphate dose can be accurately characterized, and dietary calcium data are needed to evaluate potential effects of altered calcium:phosphate ratio, which is an important determinant of phosphate toxicity. For observed health outcomes to be reliably attributed to changes in phosphate, calcium levels need to be constant across control and exposure groups.

As a result of the limitations of the available oral toxicity data for aluminum phosphates, subchronic and chronic provisional reference doses (p-RfDs) were not derived directly. Instead, subchronic and chronic screening p-RfDs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, aluminum was selected as the most appropriate analogue for aluminum phosphate salts for deriving a subchronic and chronic screening p-RfD.

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

There are no suitable human or animal data available to derive subchronic or chronic provisional reference concentrations (p-RfCs) for aluminum phosphate salts (multiple CASRNs). An alternative analogue approach was considered but not employed due to lack of relevant inhalation toxicity values for the candidate analogues and extremely limited inhalation data for aluminum phosphate salts (see Appendix A for more details).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

The noncancer provisional reference values for aluminum phosphate salts are summarized in Table 5.

Table 5. Summary of Noncancer Reference Values for Aluminum Phosphate Salts (Multiple CASRNs)							
Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF _C	Principal Study
Subchronic screening p-RfD (mg/kg-d)	Mouse/ M, F	Neurobehavioral effects (shorter latency to fall in wire suspension test [M], impaired performance in water maze [F])	3×10^{-1}	NOAEL	26 (based on analogue POD) ^a	100	Golub and Germann (2001) as cited in ATSDR (2008)
Chronic screening p-RfD (mg/kg-d)	Mouse/ M, F	Neurobehavioral effects (shorter latency to fall in wire suspension test [M], impaired performance in water maze [F])	3×10^{-1}	NOAEL	26 (based on analogue POD) ^a	100	Golub and Germann (2001) as cited in ATSDR (2008)
Subchronic p-RfC (mg/m ³)	NDr						
Chronic p-RfC (mg/m ³)	NDr						

^aBased on aluminum assessment (ATSDR 2008).

F = female(s); M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 6 identifies the cancer weight-of-evidence (WOE) descriptor for aluminum phosphate salts (multiple CASRNs). No human or animal studies evaluating cancer endpoints are available for any of the chemicals. Limited genotoxicity assays (see Table 4) for aluminum dihydrogen tripolyphosphate, aluminum orthophosphate, and aluminum metaphosphate have reported negative results. Under the [U.S. EPA \(2005\)](#) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential, and the cancer WOE descriptor for aluminum phosphate salts is “*Inadequate Information to Assess the Carcinogenic Potential*” (for both oral and inhalation routes of exposure).

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
“Carcinogenic to Humans”	NS	NA	There are no human carcinogenicity data identified to support this descriptor.
“ <i>Likely to Be Carcinogenic to Humans</i> ”	NS	NA	There are no human or animal carcinogenicity studies identified to support this descriptor.
“ <i>Suggestive Evidence of Carcinogenic Potential</i> ”	NS	NA	There are no human or animal carcinogenicity studies identified to support this descriptor.
“ <i>Inadequate Information to Assess Carcinogenic Potential</i> ”	Selected	Both	This descriptor is selected due to the lack of any information on carcinogenicity of aluminum phosphate salts.
“ <i>Not Likely to Be Carcinogenic to Humans</i> ”	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected; WOE = weight of evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Due to a lack of carcinogenicity data, derivation of cancer risk estimates is precluded (see Table 7).

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	Principal Study
p-OSF (mg/kg-d) ⁻¹	NDr			
p-IUR (mg/m ³) ⁻¹	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. NONCANCER SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, it is inappropriate to derive provisional toxicity values for aluminum phosphate salts. However, some information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a “screening value.” Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with deriving an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS)

The analogue approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for analogue analysis are presented in [Wang et al. \(2012\)](#); [Lizarraga et al. \(2023\)](#). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection. The analogue approach may or may not be route-specific or applicable to multiple routes of exposure. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable analogue both toxicologically and chemically.

An expanded analogue identification approach was developed to collect a more comprehensive set of candidate analogues for the compounds undergoing the U.S. Environmental Protection Agency (U.S. EPA) PPRTV screening-level assessment. As described below, this method includes application of a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on chemical structure and key features; metabolic relationships; or related toxic effects and mechanisms of action.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus³ ([NLM, 2021a](#)), CompTox Chemicals Dashboard ([U.S. EPA, 2021a](#)), and the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox ([OECD, 2021](#)). Additional analogues identified as ChemIDplus-related substances, parent, salts, and mixtures, and CompTox-related substances are considered. CompTox Generalized Read-Across (GenRA) analogues are collected using the methods available on the publicly available GenRA Beta version, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and ToxCast, Tox21, and ToxRef data. For compounds that have very few analogues identified by structure similarity using a similarity threshold of 0.8 or 80%, substructure searches in the QSAR Toolbox may be performed, or similarity searches may be rerun using a reduced similarity threshold

³The National Library of Medicine (NLM) retired ChemIDPlus in December 2022.

(e.g., 70 or 60%). The compiled list of candidate analogues is batch run through the CompTox Chemicals Dashboard where QSAR-ready simplified molecular-input line-entry system (SMILES) notations are collected and toxicity data availability is determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], Office of Environmental Health Hazard Assessment [OEHHA], California Environmental Protection Agency [CalEPA], the U.S. EPA Integrated Risk Information System [IRIS], PPRTVs). The batch output information is then uploaded into the Chemical Assessment Clustering Engine (ChemACE) ([U.S. EPA, 2011a](#)), which clusters the chemicals based on chemical fragments and displays the toxicity data availability for each candidate. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on known or expected structure-toxicity relationships, reactivity, and known or expected metabolic pathways.

Toxicokinetic studies tagged as potentially relevant supplemental material during screening were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches were conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical. Metabolic analogues are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, the U.S. EPA IRIS, PPRTV assessments).

In vivo toxicity data for the target chemical (if available) are evaluated to determine whether characteristic toxicity associated with a particular mechanism of toxicity was observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data tagged as potentially relevant supplemental material during screening or obtained from tools including GenRA, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) ([CTD, 2022](#); [Davis et al., 2021](#)) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox21 are collected to determine bioactivity of the target chemical in in vitro assays that may indicate potential mechanism(s) of action. The GenRA option within the Dashboard also offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified with similarity indices of ≥ 0.5 may be considered potential candidate analogues. The CTD ([CTD, 2022](#); [Davis et al., 2021](#)) is searched to identify compounds with gene interactions similar to interactions induced by the target chemical; compounds with gene interactions similar to the target chemical (with a similarity index > 0.5) may be considered potential candidate analogues. These compounds are then added to the pool of candidate analogues, and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, the U.S. EPA IRIS, PPRTV assessments).

The application of a variety of different tools and methods to identify candidate analogues serves to minimize the limitations of any individual tool with respect to the pool of chemicals included, chemical fragments considered, and methods for assessing similarity. Further, the inclusion of techniques to identify analogues based on metabolism and toxicity or bioactivity expands the pool of candidates beyond those based exclusively on structural similarity. The specific tools described above are used for the expanded analogue searches were selected because they are publicly available, supported by U.S. and OECD agencies, updated regularly, and widely used.

Analogue Search Results for Aluminum Phosphates

Because aluminum phosphates are composed entirely of inorganic components, potential structural analogues are limited to its component functional groups (i.e., the aluminum cation and inorganic phosphate anion), and there are no metabolic analogues.

Available toxicity and mechanistic data for aluminum phosphates were evaluated to determine whether these data would suggest candidate analogues. The GenRA option within the U.S. EPA CompTox Chemicals Dashboard offers an option to search for analogues based on similarities in activity in in vitro assays in ToxCast/Tox21; however, for the aluminum phosphate salts, the GenRA module returned an error message (based on insufficient data). No bioactivity data were available for aluminum phosphate compounds in the dashboard. The CTD did not have any entries for aluminum phosphates.

The available oral toxicity data for aluminum phosphates, described in the main PPRTV assessment text above, were reviewed to determine whether there were in vivo toxicity data suggesting specific, characteristic toxicity (e.g., inhibition of oxidative phosphorylation) that could be used to identify candidate analogues. The kidney has been identified as a target of aluminum phosphates-induced toxicity after oral exposure. Limited oral toxicity data in animals identified renal nephrocalcinosis and increased kidney weight in animals administered mixed sodium aluminum phosphates [Anonymous (1972) as cited in [ECHA \(1972a, 1972c, 1972e, 1972f\)](#)]. However, none of the effects identified in the limited in vivo studies suggested a characteristic or unique toxicity that could be used to suggest candidate analogues other than those identified based on structure.

Assessments are available for both aluminum and inorganic phosphate compounds. The PPRTV assessment for aluminum ([U.S. EPA, 2006](#)) and the ATSDR *Toxicological Profile for Aluminum* ([ATSDR, 2008](#)) both used studies of aluminum salts to derive oral toxicity values for aluminum that were meant to be generally applicable to aluminum compounds. Aluminum, as represented by oral toxicity values from [U.S. EPA \(2006\)](#) and [ATSDR \(2008\)](#), is therefore a candidate structural analogue for aluminum phosphates by oral exposure. Although the [U.S. EPA \(2006\)](#) also derived a chronic provisional reference concentration (p-RfC) for aluminum, it was based on inhalation of uncharacterized aluminum fumes and dusts by foundry workers. Without more specific exposure information (e.g., compounds, particle sizes), it is not possible to make the quantitative comparisons between inhalation of analogue and aluminum phosphates that form the basis for the alternative analogue approach.

For inorganic phosphates, PPRTV assessments for monovalent (sodium and potassium) salts of inorganic phosphates ([U.S. EPA, 2021d](#)) and divalent (calcium) salts of inorganic phosphates ([U.S. EPA, 2021c](#)) were identified. A PPRTV assessment for ammonium phosphates ([U.S. EPA, 2021b](#)) was not considered, because ammonium (as a dissociation product) is not expected to behave (chemically or toxicologically) in the same manner as metal ions. In addition, the screening toxicity value derived for ammonium phosphates is based on an effect (submucosal stomach inflammation) associated with the ammonium moiety of the compound. The sodium and potassium salts of inorganic phosphates and calcium salts of inorganic phosphates, which were assessed by [U.S. EPA \(2021c, 2021d\)](#), are candidate structural analogues for aluminum phosphates by oral exposure. Although IRIS lists a chronic RfC for phosphoric acid, it is based

on data for obscurant smoke aerosol combustion products of a 95% red phosphorus/5% butyl rubber mixture and is not relevant to the current assessment.

In summary, the two key structural components of aluminum phosphates, aluminum, and inorganic phosphate, are identified as candidate structural analogues with applicable oral toxicity values but no relevant inhalation toxicity values. No potential metabolic or toxicity/mechanistic analogues were identified. Due to the lack of candidate analogues with inhalation toxicity values, the alternative analogue approach was performed only for oral exposure.

Structural/Physicochemical Properties Similarity Comparisons

Although information pertaining to the physicochemical properties of aluminum phosphates and its candidate analogues is sparse, water solubility data are available (see Table A-1). Water solubility data are important for evaluating the candidate analogues because water solubility is a key determinant of bioavailability, which is discussed in the “Metabolic/Toxicokinetic Similarity Comparison” section below.

Table A-1. Water Solubility of Aluminum Phosphates and Candidate Analogues^a

Solubility	Aluminum Phosphates	Aluminum Salts	Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
Very soluble		<ul style="list-style-type: none"> Aluminum nitrate 	<ul style="list-style-type: none"> Monosodium phosphate (949 g/L) (U.S. EPA, 2021d) Monopotassium phosphate Disodium phosphate Trisodium phosphate Dipotassium phosphate Tripotassium phosphate Tetrapotassium pyrophosphate Potassium tripolyphosphate Sodium acid pyrophosphate Tetrasodium pyrophosphate Sodium tripolyphosphate Sodium trimetaphosphate 	
Soluble		<ul style="list-style-type: none"> Aluminum lactate (4.67 g/L) (http://www.vcclab.org/lab/alogps/) Aluminum sulfate Aluminum chlorohydrate 	<ul style="list-style-type: none"> Sodium polyphosphate Sodium hexametaphosphate 	
Moderate solubility				<ul style="list-style-type: none"> Dicalcium phosphate (153 mg/L) (U.S. EPA, 2021c) Monocalcium phosphate
Slightly or sparingly soluble	<ul style="list-style-type: none"> Monoaluminum phosphate Sodium aluminum phosphate anhydrous (basic SALP) 	<ul style="list-style-type: none"> Aluminum fluoride Aluminum potassium sulfate 		<ul style="list-style-type: none"> Tricalcium phosphate ≤20 mg/L (U.S. EPA, 2021c)
Insoluble or negligible solubility	<ul style="list-style-type: none"> Aluminum phosphate Aluminum metaphosphate Aluminum triphosphate Sodium aluminum phosphate tetrahydrate (SALP) Sodium aluminum phosphate acidic (acidic SALP) 	<ul style="list-style-type: none"> Aluminum hydroxide Aluminum carbonate 		<ul style="list-style-type: none"> Calcium pyrophosphate

Table A-1. Water Solubility of Aluminum Phosphates and Candidate Analogues^a

Solubility	Aluminum Phosphates	Aluminum Salts	Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
Soluble at low pH	<ul style="list-style-type: none"> • Monoaluminum phosphate • Aluminum phosphate (slightly) 	<ul style="list-style-type: none"> • Aluminum hydroxide • Aluminum carbonate • Aluminum fluoride (sparingly) 		<ul style="list-style-type: none"> • Monocalcium phosphate • Dicalcium phosphate (moderate) • Calcium pyrophosphate (slightly)

^aAssignment of aluminum salts, sodium and potassium salts of inorganic phosphates, and calcium salts of inorganic phosphates to solubility categories was based on qualitative or quantitative data provided in existing assessments ([U.S. EPA, 2021c, d](#); [ATSDR, 2008](#); [U.S. EPA, 2006](#)). For quantitative data, the following criteria were used (mg/L): >10,000 = very soluble, >1,000–10,000 = soluble, >100–10,000 = moderately soluble, >0.1–100 = slightly soluble, and <0.1 = negligible solubility.

Bold indicates that data for the compound were used to derive a toxicity value.

SALP = sodium aluminum phosphate.

The target compounds, aluminum phosphates, are slightly soluble or insoluble in water. Although the solubility of some aluminum phosphates is increased at low pH (e.g., monoaluminum phosphate), solubility at biological pH remains low ([Schrödter et al., 2012](#); [ATSDR, 2008](#)).

Aluminum salts, which form the basis for the ATSDR assessment for aluminum and compounds ([ATSDR, 2008](#)) and the PPRTV assessment for aluminum ([U.S. EPA, 2006](#)), range from insoluble to very soluble in water and are expected to exhibit increased solubility under acidic conditions. As shown in Table A-1, aluminum salts are at least as soluble as aluminum phosphate salts. Aluminum lactate, the compound used to derive toxicity values for aluminum and compounds, is freely soluble in water.

With respect to inorganic phosphates, sodium and potassium salts of inorganic phosphates are soluble in water ([U.S. EPA, 2021d](#)). Monosodium phosphate (MSP), the compound used to derive toxicity values for sodium and potassium phosphate salts, exhibits moderate solubility in water. Calcium phosphate salts are less water-soluble than sodium and potassium phosphate salts. The water solubility of calcium phosphate salts ranges from practically insoluble to moderately soluble. The solubility of calcium phosphate salts is enhanced in acidic conditions relative to neutral or basic solutions ([U.S. EPA, 2021c](#)). The calcium phosphate salts used to derive the toxicity value, dicalcium phosphate (DCP) and tricalcium phosphate (TCP), are slightly soluble in water ([U.S. EPA, 2021c](#)).

Solubility data suggest that aluminum salts, sodium and potassium salts of inorganic phosphates, and calcium salts of inorganic phosphates are suitable analogues for aluminum phosphates because these compounds are as soluble as, or more soluble than, aluminum phosphates. Based on solubility considerations alone, aluminum and sodium and potassium phosphate salts are more health-protective choices than calcium phosphate salts because the water solubility of these compounds (i.e., the compounds used to derive toxicity values) is higher than that of calcium phosphate salts.

Metabolic/Toxicokinetic Similarity Comparisons

Candidate analogues for aluminum phosphates have oral toxicity values, but no inhalation toxicity values that are relevant to this assessment. Thus, comparison of toxicokinetic data for aluminum phosphates and candidate analogues will focus on the oral route of exposure. In addition, since toxicity is partly a function of the amount of the compound that reaches the target, the focus will be the absorption and bioavailability of the aluminum and phosphate moieties from aluminum phosphates and the candidate analogues. There are no data to indicate that aluminum phosphates or candidate analogues (as inorganic compounds) are substantially metabolized. Absorption, distribution, metabolism, and excretion (ADME) data for aluminum phosphates and candidate analogues are presented in Table A-2 and discussed below.

Table A-2. Comparison of ADME Data for Aluminum Phosphates and Candidate Analogues^a

Aluminum Phosphates (target) ^b	Aluminum and Compounds (aluminum moiety)	Sodium and Potassium Phosphate Salts (phosphate moiety)	Calcium Phosphate Salts (phosphate moiety)
Absorption			
<ul style="list-style-type: none"> • Poor absorption of aluminum from aluminum phosphates (0.1–0.3% based on studies in rats) • Absorption and bioavailability influenced by chemical form, pH, ingestion of other ligands. • Bioavailability of aluminum low; aluminum phosphates sparingly soluble or insoluble. 	<ul style="list-style-type: none"> • Aluminum is poorly absorbed (ranging from 0.1 to 5% based on studies in humans and animals). • Absorption and bioavailability can vary substantially (as much as 10-fold) based on chemical form, pH, caloric state, and/or ingestion of other ligands. • Ligands enhance absorption by forming absorbable complexes (e.g., carboxylic acids) or reduce absorption by forming insoluble compounds. • Bioavailability expected to parallel water solubility (excluding other factors). 	<ul style="list-style-type: none"> • Moderate to high absorption. • Bioavailability expected to parallel water solubility. • Bioavailability depends on amount of co-ingested calcium, also food source (animal or plant). 	<ul style="list-style-type: none"> • Low to moderate absorption. • Reduced absorption owing to the interaction of free phosphorus and calcium in the intestine. • Bioavailability expected to parallel water solubility.
Distribution			
<ul style="list-style-type: none"> • Low amounts of bioavailable aluminum distributed throughout body. • Little to no evidence for aluminum deposition in bone (based on studies in rodents and dogs). 	<ul style="list-style-type: none"> • Bioavailable aluminum distributed throughout body (e.g., bone, brain, kidney). • Evidence for aluminum deposition to bone (based on animal studies). 	<ul style="list-style-type: none"> • Phosphate distributed throughout the body. 	<ul style="list-style-type: none"> • Phosphate distributed throughout the body.
Metabolism			
ND	ND	ND	ND

Table A-2. Comparison of ADME Data for Aluminum Phosphates and Candidate Analogues^a

Aluminum Phosphates (target)^b	Aluminum and Compounds (aluminum moiety)	Sodium and Potassium Phosphate Salts (phosphate moiety)	Calcium Phosphate Salts (phosphate moiety)
Excretion			
<ul style="list-style-type: none"> Aluminum excreted primarily in the urine; also in bile. 	<ul style="list-style-type: none"> Aluminum excreted primarily in the urine; also in bile. 	<ul style="list-style-type: none"> Phosphate excreted in both the urine and feces. 	<ul style="list-style-type: none"> Phosphate excreted in both the urine and feces. Urinary excretion of phosphate can be reduced due to the interaction of phosphate and calcium in the kidney.

^aData for aluminum salts, sodium and potassium salts of inorganic phosphates, and calcium salts of inorganic compounds are from existing assessments ([U.S. EPA, 2021c, d](#); [ATSDR, 2008](#); [U.S. EPA, 2006](#)).

^bADME data were only available for the aluminum moiety from aluminum phosphates.

ADME = absorption, distribution, metabolism, and excretion; ND = no data.

Data on the absorption of aluminum phosphates are limited to the aluminum moiety. The aluminum moiety of aluminum phosphates is poorly absorbed (about 0.1–0.3% based on studies in rats). The bioavailability of aluminum from aluminum phosphates is low owing to their limited solubility ([Younes et al., 2018](#); [Willhite et al., 2014](#); [Greger, 1993](#)). Absorption is influenced by chemical form, pH of the gastrointestinal tract (higher solubility at low pH), and the consumption of other foods (e.g., that alter acidity) ([Younes et al., 2018](#); [Greger et al., 1997](#); [Berthon and Daydé, 1992](#); [Daydé et al., 1990](#)). The small amounts of free aluminum that are generated at low pH in the stomach can complex with its original anion (forming largely insoluble compounds) or other dietary constituents. Free aluminum that reaches the higher pH environment of the intestine predominantly leads to the formation of insoluble aluminum hydroxide ([ATSDR, 2008](#)). Low amounts of absorbed aluminum are distributed throughout the body. However, there is little to no evidence for the deposition of aluminum from aluminum phosphates in bone, a tissue in which aluminum is known to accumulate.

For aluminum salts other than aluminum phosphates, data indicate that the aluminum moiety is poorly absorbed via the oral route of exposure (albeit not as poorly as the aluminum moiety from aluminum phosphates). Absorption of aluminum from aluminum salts is estimated to range from 0.1 to 5% based on studies in humans and animals ([ATSDR, 2008](#); [U.S. EPA, 2006](#)). As is the case for aluminum phosphates, the absorption and bioavailability of aluminum varies based on the chemical form administered, pH, caloric status, and/or the presence of ligands. Ligands can enhance absorption by forming absorbable complexes (e.g., carboxylic acids) or reduce absorption by forming insoluble compounds ([ATSDR, 2008](#); [U.S. EPA, 2006](#)). Excluding these other factors, the bioavailability of the aluminum moiety from aluminum phosphates is expected to parallel water solubility ([ATSDR, 2008](#)); therefore, the aluminum moiety from other aluminum salts is likely more bioavailable than the aluminum moiety from aluminum phosphates. Bioavailable aluminum is distributed throughout the body (e.g., bone, brain, kidney). There is evidence from animal studies that levels of aluminum in bone are increased after administration of other aluminum salts (including aluminum lactate) ([ATSDR, 2008](#)).

Data for inorganic phosphates (sodium and potassium phosphate salts and calcium phosphate salts) indicate that inorganic phosphate is readily absorbed from the gastrointestinal tract. Calcium phosphate salts are more soluble at low pH (e.g., the stomach); neutralization of the pH in the intestines leads to reductions in solubility and absorption of phosphate ([U.S. EPA, 2021c](#)). For sodium, potassium, and calcium phosphate salts, absorption of the phosphate moiety depends on the amount of calcium present, because calcium and phosphate bind in the intestine, leading to decreased phosphate absorption ([U.S. EPA, 2021c, d](#)). In general, the bioavailability of phosphate from sodium and potassium phosphate salts (including MSP) and calcium phosphate salts (including DCP and TCP) is expected to be higher than that from aluminum phosphates because they are more soluble. Further, because bioavailability is expected to parallel water solubility, the bioavailability of the phosphate moiety is expected to be higher from sodium and potassium phosphate salts than calcium phosphate salts ([U.S. EPA, 2021c, d](#)).

Toxicokinetic data suggest that aluminum (from aluminum salts) is a suitable analogue for aluminum phosphates because the aluminum moiety from other aluminum salts is expected to be absorbed at least as much or more than the aluminum moiety from aluminum phosphates. Similarly, the phosphate moiety from sodium and potassium phosphate salts and calcium

phosphate salts is expected to be more absorbed and more bioavailable than the phosphate moiety from aluminum phosphates (with sodium and potassium phosphate salts having a greater expected absorption and bioavailability of the phosphate moiety than calcium phosphate salts). Therefore, the available metabolism data suggest that aluminum and phosphate salts are plausible metabolic analogues for the target.

Toxicodynamic Similarity Comparisons

Table A-3 summarizes available oral toxicity values for the candidate analogues of aluminum phosphates. No inhalation toxicity values relevant to this assessment were identified for the candidate analogues. The database considered suitable for the derivation of subchronic and chronic toxicity values for aluminum phosphates and candidate analogues (e.g., studies of an appropriate duration and including information on the baseline diet) consists predominantly of oral toxicity studies in animals. Table A-4 shows the lowest lowest-observed-adverse-effect levels (LOAELs) or highest no-observed-adverse-effect levels (NOAELs) for the target organ or systems which served as the basis for the derivation of subchronic or chronic toxicity values for the candidate analogues.

Table A-3. Comparison of Available Oral Toxicity Data for Aluminum Phosphates and Candidate Analogues				
Chemical	Aluminum Phosphates^a (target)	Aluminum (and compounds)	Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
CASRN	Multiple	Multiple	Multiple	Multiple
Subchronic oral toxicity values				
POD	ND	26 mg Al/kg-d (as aluminum lactate)	120 mg P/kg-d (as monosodium phosphate)	240 mg DCP or TCP/kg-d (48–50 mg P/kg-d) ^b
POD type	ND	NOAEL	LOAEL	NOAEL
Subchronic UF _C and MF (component uncertainty factors)	ND	100 (10 for UF _A , 10 for UF _H); MF of 0.3	30	30
Subchronic p-RfD/MRL	ND	1 mg Al/kg-d	4 mg P/kg-d	8 mg DCP or TCP/kg-d (1.6–1.8 mg P/kg-d) ^c
Critical effects	ND	Neurobehavioral effects (impaired performance in water maze [F], shorter latency to fall in wire suspension test [M])	Nephrocalcinosis	No treatment-related effects
Species	ND	Mouse	Rabbit	Rat
Duration	ND	During gestation, lactation, and PNDs 21–35	8 wk	28 d or during pre-mating, mating, gestation, and lactation
Route (method)	ND	Oral (diet)	Oral (diet)	Oral (gavage)
Source	NA	Golub and Germann (2001) as cited in ATSDR (2008)	U.S. EPA (2021d) ; Ritskes-Hoitinga et al. (2004)	NIER (2007, 2009, 2010) as cited in U.S. EPA (2021c)
Chronic oral toxicity values				
POD	ND	100 mg Al/kg-d (as aluminum lactate)	120 mg P/kg-d (as monosodium phosphate)	ND
POD type	ND	LOAEL	LOAEL	ND
Subchronic UF _C and MF (component uncertainty factors)	ND	100 (10 for UF _A , 3 for UF _H , 3 for UF _L)	300 (10 for UF _A , 10 for UF _H , 3 for UF _L); MF ^d of 0.3	ND

Table A-3. Comparison of Available Oral Toxicity Data for Aluminum Phosphates and Candidate Analogues

Chemical	Aluminum Phosphates ^a (target)	Aluminum (and compounds)		Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
Chronic p-RfD/MRL	ND	1 mg Al/kg-d		1 mg P/kg-d	ND
Critical effects	ND	Neurobehavioral effects (changes in forelimb and hindlimb strength, increased foot splay)	Neurobehavioral effects (reductions in forelimb and hindlimb strength and thermal sensitivity)	Nephrocalcinosis	ND
Species	ND	Mouse		Rabbit	ND
Duration	ND	During gestation and lactation and/or maturity	Conception to 24 mo	8 wk	ND
Route (method)	ND	Oral (diet)		Oral (diet)	ND
Source	NA	U.S. EPA (2006) ; Golub et al. (1995) ; Donald et al. (1989)	Golub and Germann (2001) as cited in ATSDR (2008)	U.S. EPA (2021d) ; Ritskes-Hoitinga et al., 2004	NA

^aNo toxicity values were derived for aluminum phosphates due to limitations associated with the available database (data that could not be independently verified, inadequate information on the content of baseline diets, studies conducted by a laboratory OECD deemed unreliable, and small sample sizes).

^bDoses in mg P/kg-day calculated based on the following molecular weights (in g/mol): P = 30.974, DCP = 136.056, and TCP = 310.174.

^cScreening-level value.

^dA modifying factor of 0.3 was used by ATSDR to account for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

DCP = dicalcium phosphate; F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MF = modifying factor; MRL = minimal risk level; NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; OECD = Organisation for Economic Co-operation and Development; P = phosphorus; PND = postnatal day; POD = point of departure; p-RfD = provisional reference dose; TCP = tricalcium phosphate, UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor

Table A-4. Comparison of Effects Following Oral Exposure to Aluminum Phosphates and Candidate Analogues

Target Organ/System	Aluminum Phosphates (target)	Aluminum and Compounds	Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
	Effect (species) ^{a,b}			
Body weight	NOAEL = 2,471 mg basic SALP/kg-d (320 mg Al/kg-d ^c); diet for 28 d (rat [M]), Hicks et al. (1987)	≥130 mg Al/kg-d as aluminum lactate ↓ Body-weight gain; diet for 6 wk (mouse [Golub et al. (1989) as cited in U.S. EPA (2006)], rat)	≥980 mg P/kg-day as MKP ↓ Body weight; diet for 8 wk (rat), Huttunen et al. (2007) as cited in U.S. EPA (2021d)	NOAEL = 1,000 mg DCP or TCP/kg-d (200–230 mg P/kg-d ^c); gavage for 28 d or during pre-mating, mating, gestation, and until LD 4 (rat), NIER (2007) as cited in U.S. EPA (2021c)
Kidney	≥694 mg basic or acidic SALPs/kg-d (≥56 mg Al/kg-d ^c) Nephrocalcinosis; diet for 90 d (rat [F], ECHA (1972e) ; dog) ^d	NOAEL = 284 mg Al/kg-d as aluminum nitrate; drinking water for 100 d (rat), Domingo et al. (1987) as cited in U.S. EPA (2006)	≥290 mg P/kg-d as MSP dihydrate Nephrocalcinosis; diet for 4 or 8 wk (rat [F]; rabbit [M]), Ritskes-Hoitinga et al. (2004)	NOAEL = 1,000 mg DCP or TCP/kg-d (200–230 mg P/kg-d ^c); gavage for 28 d or during pre-mating, mating, gestation, and until LD 4 (rat), NIER (2007) as cited in U.S. EPA (2021c)
Neurological	ND	≥130 mg Al/kg-d as aluminum lactate ↓ Motor activity; diet for 6 wk (mouse [Golub et al. (1989) as cited in U.S. EPA (2006)], rat)	NOAEL = 1,100 mg P/kg-d as MKP; diet for 14 wk (rat), Abuduli et al. (2016) as cited in U.S. EPA (2021d)	NOAEL = 1,000 mg DCP or TCP/kg-d (200–230 mg P/kg-d ^c); gavage for 28 d or during pre-mating, mating, gestation, and until LD 4 (rat), NIER (2007) as cited in U.S. EPA (2021c)
Reproductive	NOAEL = 1,000 mg triphosphoric acid aluminum salt/kg-d (96 mg Al/kg-d or 330 mg P/kg-d ^c); gavage during pre-mating, mating, gestation, and until LD 4 (rat), Anonymous (2002) as cited ECHA (2002d)	155 mg Al/kg-d as aluminum lactate Altered gestational length; diet from GD 1 to LD 21 (mouse), Donald et al. (1989)	ND	NOAEL = 1,000 mg DCP or TCP/kg-d (200–230 mg P/kg-d ^c); gavage during pre-mating, mating, gestation, and until LD 4 (rat), NIER (2007) as cited in U.S. EPA (2021c)

Table A-4. Comparison of Effects Following Oral Exposure to Aluminum Phosphates and Candidate Analogues

Target Organ/System	Aluminum Phosphates (target)	Aluminum and Compounds	Sodium and Potassium Phosphate Salts	Calcium Phosphate Salts
Developmental	NOAEL = 1,000 mg triphosphoric acid aluminum salt/kg-d (96 mg Al/kg-d or 330 mg P/kg-d ^c); gavage during pre-mating, mating, gestation, and until LD 4 (rat), Anonymous (2002) as cited in ECHA (2002d)	≥100 mg Al/kg-d as aluminum lactate Neurobehavioral effects; diet during gestation and lactation and/or maturity or conception to 24 mo (mouse, rat), Golub et al. (1995)	ND	NOAEL = 1,000 mg DCP or TCP/kg-d (200–230 mg P/kg-d ^c); gavage during pre-mating, mating, gestation, and until LD 4 (rat, mouse rabbit), NIER (2007) as cited in U.S. EPA (2021c)

^aLowest LOAEL or highest NOAEL for effects on the target organ/system; ≥ indicates that other effects were reported at doses equal to or greater than the lowest LOAEL.

^bLists all species in which effects on the target organ/system were observed. The lowest LOAEL corresponds to the first species listed.

^cDoses in mg P/kg-day or mg Al/kg-day were calculated based on the following molecular weights (in g/mol): Al = 26.9815, P = 30.974, DCP = 136.056, TCP = 310.174, and triphosphoric acid aluminum salt = 281.909. Basic SALPs were provided only as trade names (e.g., KasalTM, KasalTMII). KasalTM is a mixture of alkaline sodium aluminum phosphate and dibasic sodium phosphate. The Al content (6–13%) of these basic SALPs was provided in the study report (doses in mg Al/kg-day could be estimated); however, P content was not provided and could not be reliably determined (doses in mg P/kg-day could not be estimated).

^dLOAELs for kidney effects in rats were identified only tentatively. LOAELs are for comparison purposes only; the reported data are not considered a suitable comparison for quantitative evaluation. There is low confidence in these studies, due to demonstrated poor reliability of the performing laboratory (IBT) and limitations of the available secondary source.

↑ = increased; ↓ = decreased; Al = aluminum; DCP = dicalcium phosphate; DKP = dipotassium phosphate; F = female(s); GD = gestation day; IBT = Industrial Bio-Test Laboratories, Inc.; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); MKP = monopotassium phosphate; MSP = monosodium phosphate; ND = not determined; NOAEL = no-observed-adverse-effect level; P = phosphorus; SALP = sodium aluminum phosphate; SHMP = sodium hexametaphosphate; TCP = tricalcium phosphate.

The limitations of the available data for aluminum phosphates described in the main PPRTV assessment text include studies that did not provide data or were available only from secondary sources (precluding independent review), limited presentation of data (studies in dogs), and/or absent information on the phosphate and/or calcium content of the baseline diets. Existing studies of acidic and basic sodium aluminum phosphates (SALPs) are not considered suitable for quantitative evaluation owing to demonstrated poor reliability of the performing laboratory and limitations of the available secondary source (see footnote in Table A-4). The available data for aluminum phosphates identified nephrocalcinosis as a sensitive toxicological effect (see Table A-4). The same effect was identified for sodium and potassium phosphate salts but not for the aluminum salts, suggesting that the observed renal toxicity is likely mediated by the phosphate moiety. There is no evidence for effects attributed to aluminum; however, none of the studies included a neurotoxicity evaluation. This is identified as a data gap.

Data for other aluminum salts were adequate to evaluate aluminum toxicity following oral exposure. The database contains five subchronic studies (rats and mice), four developmental studies in mice, and one multi-generation reproductive study in mice. The most sensitive toxicological effects identified were neurotoxicity and developmental effects; neurodevelopmental effects were the critical effects for the derivation of toxicity values ([ATSDR, 2008](#); [U.S. EPA, 2006](#)). These effects were observed consistently in rats and mice.

With respect to the inorganic phosphates, reliable toxicity data for sodium and potassium phosphate salts (i.e., studies that identified calcium and phosphate levels in the baseline diet) identified a LOAEL for nephrocalcinosis (the critical effect); this effect was observed in short-term and subchronic studies of rats and rabbits. Toxicity studies (mostly unpublished) for calcium phosphate salts included a 28-day repeated-dose study, a reproductive/developmental screening test, a combined repeated-dose with reproductive/developmental toxicity study, and developmental toxicity studies, none of which reported any treatment-related effects. A screening-level toxicity value was derived for calcium phosphate salts based on the absence of effects.

The available toxicity data are sparse, limiting the conclusions that can be drawn based on these data. The most sensitive effects associated with exposure to aluminum salts (neurotoxicity and neurodevelopmental toxicity) were not observed in studies of aluminum phosphates. This might reflect low uptake and bioavailability of the aluminum moiety from aluminum phosphates. However, it may also be due to database limitations for aluminum phosphates, including the lack of available studies of appropriate design to identify these types of effects and the poor quality of many of the existing studies. The most sensitive effect identified for sodium and potassium phosphate salts is nephrocalcinosis, which was also the only effect observed in studies of aluminum phosphate, suggesting that the phosphate moiety is responsible for the effect. No treatment-related effects, including nephrocalcinosis, were seen in studies of calcium phosphate salts. This likely reflects the lower uptake and bioavailability of calcium phosphate salts relative to the sodium and potassium phosphate salts.

Weight-of-Evidence Approach

A tiered WOE approach as described in [Wang et al. \(2012\)](#) and [Lizarraga et al. \(2023\)](#) was used to select the overall best analogue chemical. The approach focuses on identifying a preferred candidate for three types of analogues: structural analogues, toxicokinetic or metabolic analogues, and toxicity-like analogues. Selection of the overall best analogue chemical is then

based on all of the information from the three analogue types, and the following considerations used in a WOE approach: (1) lines of evidence from the U.S. EPA assessments are preferred; (2) biological and toxicokinetic data are preferred over the structural similarity comparisons; (3) lines of evidence that indicate pertinence to humans are preferred; (4) chronic studies are preferred over subchronic studies when selecting an analogue for a chronic value; (5) chemicals with more conservative/health-protective toxicity values may be favored; and (6) if there are no clear indications as to the best analogue chemical based on the other considerations, then the candidate analogue with the most structural similarity may be preferred.

Water solubility data indicate that aluminum phosphates are less soluble than other aluminum salts (including aluminum lactate, which serves as the basis for the toxicity values for aluminum) and also less soluble than sodium and potassium phosphate salts (including MSP, used to derive the toxicity values for these compounds) and calcium phosphate salts (including DCP and TCP, used to derive the toxicity values for these compounds). Toxicokinetic data suggest that absorption from the gastrointestinal tract and bioavailability parallel water solubility. Therefore, the aluminum moiety from aluminum phosphates is expected to be less bioavailable than the aluminum moiety from other aluminum salts, and the phosphate moiety from aluminum phosphates is expected to be less bioavailable than the phosphate moiety from sodium and potassium phosphate salts, and to a lesser extent, calcium phosphate salts. Data from animal studies detected little to no accumulation of aluminum in bone following administration of aluminum phosphates; however, aluminum was found in the bone of animals administered other aluminum salts (including aluminum lactate). This indicates that aluminum (from aluminum salts) and sodium and potassium phosphate salts and calcium phosphate salts are all appropriately conservative analogues for aluminum phosphates based on physicochemical properties and toxicokinetics (with aluminum and/or sodium and potassium phosphate salts being more protective choices than calcium phosphate salts).

The available toxicity data provide limited additional information to evaluate the suitability of the candidate analogues. No effects of aluminum (e.g., neurotoxicity, neurodevelopmental toxicity) were observed in studies of aluminum phosphates, possibly reflecting low uptake and bioavailability of the aluminum moiety from aluminum phosphates. However, this is also possibly due to limitations of the database for aluminum phosphates (lack of studies designed to identify neurotoxic effects and poor study quality). Nephrocalcinosis was the only effect observed following exposure to aluminum phosphates and is the most sensitive effect for sodium and potassium phosphate salts. This commonality in the toxicologically relevant effect suggests that the phosphate moiety is responsible for the effect. In contrast, no effects were observed in studies of calcium phosphate salts at doses much higher than that of sodium and potassium phosphate salts causing nephrocalcinosis, likely reflecting the lower uptake and bioavailability of calcium phosphate salts relative to the sodium and potassium phosphate salts, and suggesting that calcium phosphate salts would be a less suitable analogue for aluminum phosphate.

Taken together, the water solubility, bioavailability, and toxicity data indicate that aluminum (from aluminum salts) and sodium and potassium phosphate salts are the most suitable analogues for aluminum phosphates. Although there are toxicity data that indicate that nephrocalcinosis, likely mediated by the phosphate moiety, was observed following aluminum phosphate exposure (and no effects attributed to aluminum), the available database for aluminum phosphates does not adequately evaluate the neurological/neurodevelopmental endpoints

associated with aluminum toxicity; this deficiency is considered a data gap. To adequately protect against all of the potential effects mediated by both the aluminum moiety and the phosphate moiety of aluminum phosphates (and given the data gaps for neurotoxic and developmental effects), the candidate analogue with the most conservative toxicity value is selected as the most suitable analogue. The intermediate minimum risk level (MRL)/chronic provisional reference dose (p-RfD) value of 1 mg Al/kg-day for aluminum compounds ([ATSDR, 2008](#)) is lower than the subchronic p-RfD value of 4 mg P/kg-day for sodium and potassium phosphate salts ([U.S. EPA, 2021d](#)). However, aluminum phosphate compounds typically contain more phosphate than aluminum. The molar ratio of aluminum to inorganic phosphate is between 1:1 and 1:3 for most of the included aluminum phosphate salts (and did not exceed 1:4 for any compound; see Table A-5). Comparing the toxicity values on a molar basis (i.e., 1 mg Al/kg-day equivalent mol of aluminum to 4 mg P/kg-day equivalent mol of phosphorus) yields a ratio of 1:3.5 aluminum:phosphorus (calculated using molecular weights for aluminum and phosphorus of 26.982 and 30.974 g/mol, respectively), higher than all but one of the included aluminum phosphate compounds ($\text{Al}_2\text{H}_{15}\text{Na}_3\text{O}_{32}\text{P}_8$, with ratio of 1:4)). Thus, using aluminum as an analogue will be more protective. For example, the reference dose (RfD) of 1 mg Al/kg-day is equivalent to 11.8 mg $\text{AlH}_6\text{O}_{12}\text{P}_3$ /kg-day (with aluminum to inorganic phosphate molar ratio of 1:3), and the RfD of 4 mg P/kg-day is equivalent to 13.7 mg $\text{AlH}_6\text{O}_{12}\text{P}_3$ /kg-day.⁴ Therefore, selection of aluminum as the analogue is expected to be protective for aluminum phosphate salts collectively, both for effects of aluminum and effects of inorganic phosphate. Aluminum (from aluminum salts) is identified as the most appropriate analogue for aluminum phosphates for the subchronic RfD. Although the chronic RfD of sodium and potassium phosphate salts is 1 mg P/kg-day ([U.S. EPA, 2021d](#)), which is equivalent to 3.4 mg $\text{AlH}_6\text{O}_{12}\text{P}_3$ /kg-day, considering a much higher water solubility (869 g/L) of the sodium phosphate used to derive the RfD for sodium and potassium phosphate salts ([U.S. EPA, 2021d](#)) than that of the aluminum lactate (4.67 g/L) used to derive the RfD for aluminum compounds, the POD based on aluminum compounds is still expected to be protective for chronic exposure to aluminum phosphate.

Table A-5. Aluminum: Phosphate Molar Ratio of Aluminum Phosphates and Mixed Sodium Aluminum Phosphates

Compound [synonym]	CASRN	Molecular Formula ^a	Molar Ratio Al:P
Phosphoric acid, aluminum salt (1:1) [aluminum phosphate]	7784-30-7	AlO_4P	1:1
Metaphosphoric acid (HPO_3), aluminum salt (3:1) [aluminum metaphosphate]	13776-88-0	AlO_9P_3	1:3
Triphosphoric acid, aluminum salt (1:1) [aluminum triphosphate]	13939-25-8	$\text{AlH}_2\text{O}_{10}\text{P}_3$	1:3
Phosphoric acid, aluminum salt (3:1) [monoaluminum phosphate; aluminum dihydrogenphosphate]	13530-50-2	$\text{AlH}_6\text{O}_{12}\text{P}_3$	1:3

⁴1 mg Al/kg-day = $317.939 (\text{AlH}_6\text{O}_{12}\text{P}_3) \div 26.981(\text{Al}) = 11.8 \text{ mg } \text{AlH}_6\text{O}_{12}\text{P}_3/\text{kg-day}$.

4 mg P/kg-day = $4 \times [317.939 (\text{AlH}_6\text{O}_{12}\text{P}_3) \div (30.974 \times 3) (\text{P})] = 13.7 \text{ mg } \text{AlH}_6\text{O}_{12}\text{P}_3/\text{kg-day}$.

Table A-5. Aluminum: Phosphate Molar Ratio of Aluminum Phosphates and Mixed Sodium Aluminum Phosphates

Compound [synonym]	CASRN	Molecular Formula ^a	Molar Ratio Al:P
Phosphoric acid, aluminum sodium salt (8:3:1), tetrahydrate [sodium aluminum phosphate tetrahydrate (SALP)]	10305-76-7	Al ₃ H ₂₂ NaO ₃₆ P ₈	3:8
Phosphoric acid, aluminum sodium salt (8:2:3) [sodium aluminum phosphate anhydrous (basic SALP)]	10279-59-1	Al ₂ H ₁₅ Na ₃ O ₃₂ P ₈	1:4
Phosphoric acid, aluminum sodium salt (1:?:?) [sodium aluminum phosphate acidic (acidic SALP)]	7785-88-8	Mixture of Al ₃ H ₂₂ NaO ₃₆ P ₈ and Al ₂ H ₁₅ Na ₃ O ₃₂ P ₈	NA
Phosphoric acid, aluminum sodium salt (8:3:1) [trialuminum sodium tetra- decahydrogenoctaorthophosphate]	15136-87-5	Al ₃ H ₁₄ NaO ₃₂ P ₈	3:8

^a[U.S. EPA \(2021a\)](#).

NA = not applicable; SALP = sodium aluminum phosphate.

ORAL NONCANCER TOXICITY VALUES

Derivation of a Subchronic Screening Provisional Reference Dose

Based on the overall analogue approach presented in this PPRTV assessment, aluminum was selected as the analogue for aluminum phosphates for derivation of subchronic and chronic screening p-RfDs. The study used for the U.S. EPA subchronic screening p-RfD value for aluminum phosphates is a developmental toxicity study of aluminum lactate in mice [Golub and Germann (2001) as cited in [ATSDR \(2008\)](#)]⁵. [ATSDR \(2008\)](#) provided the following summary:

Groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On postnatal day (PND) 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the recommended dietary allowance (RDA); these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by

⁵Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice. *Neurotoxicol Teratol* 23(4):365-372. ([as cited in ATSDR, 2008](#))

the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests.

No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg Al/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was statistically significant at 260 mg Al/kg/day. On PND 90, female mice in the 260 mg Al/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg Al/kg/day in the females. Also, increases in absolute brain weight were observed in females at 26 mg Al/kg/day and relative brain weights were observed at 26 or 260 mg Al/kg/day, but not at 130 mg Al/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg Al/kg/day at 5 months; an increase in food intake was also observed at these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg Al/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg Al/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg Al/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg Al/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg Al/kg/day, an increase in the number of rotations on the rotorod as observed at 260 mg Al/kg/day, and a shorter latency to fall in the wire suspension test was observed at 130 and 260 mg Al/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls; the number of rotations was still significantly different from control after adjustment for body weight.

The NOAEL of 26 mg Al/kg-day was selected as the point of departure (POD) for aluminum based on neurobehavioral effects; namely a shorter latency to fall from the wire in males (wire suspension test) and increased latency to locate the platform following cue relocation in females (Morris water maze) at 130 mg Al/kg-day (LOAEL). Benchmark dose (BMD) modeling with Benchmark Dose Software (BMDS; version 3.2) could not be conducted for latency to fall from the wire because the measure of variance provided in the study (i.e., standard error of the mean [SEM] or standard deviation [SD]) was not specified. Data for the change in latency to find the platform were modeled using 1 SD from controls as the benchmark response (BMR). The constant variance linear model provided an adequate fit to the data; however, the BMD and the 95% benchmark dose lower confidence limit (BMDL) were higher than the LOAEL for latency to fall (and were therefore not considered appropriate for use as the POD). Human equivalent doses (HEDs) were not calculated.

The intermediate MRL (analogous to a subchronic p-RfD) of 1 mg Al/kg-day was derived from the NOAEL of 26 mg Al/kg-day using a composite uncertainty factor (UF_C) of 100, reflecting 10-fold uncertainty factors for interspecies extrapolation (UF_A) and intraspecies variability (UF_H). [ATSDR \(2008\)](#) also applied a modifying factor (MF) of 0.3:

...to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

[Wang et al. \(2012\)](#) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the analogue unless additional information is available. ATSDR methodology did not include application of a database uncertainty factor (UF_D), so none was assigned in deriving the intermediate oral MRL for aluminum. Because in the Golub and Germann (2001) as cited in [ATSDR \(2008\)](#) study, the animals were not only exposed to the aluminum during gestation, but also during lactation, an HED for the POD of 26 mg/kg-day was not calculated for the current assessment for aluminum phosphates, consistent with the U.S. EPA guidelines ([U.S. EPA, 2011c](#)). A UF_C of 100 was applied based on a 10-fold UF_A and 10-fold UF_H. A UF_D of 1 was used because the database for aluminum compounds includes multiple studies identifying neurotoxicity and neurodevelopmental toxicity as sensitive effects in rodents. Although no studies of aluminum phosphates specifically evaluated neurological endpoints, an increase in this uncertainty factor was not considered necessary because the aluminum moiety from aluminum phosphates (insoluble in water or slightly soluble at low pH, see Table 1) is expected to be less bioavailable than the aluminum moiety from other aluminum salts (i.e., aluminum lactate used as the basis for analogue POD is soluble in water and its bioavailability is higher than most of the aluminum compounds typically found in drinking water or diet).

$$\begin{aligned}
 \text{Subchronic Screening p-RfD} &= \text{Analogue POD} \div \text{UF}_C \\
 &= 26 \text{ mg Al/kg-day} \div 100 \\
 &= \mathbf{3 \times 10^{-1} \text{ mg Al/kg-day}}
 \end{aligned}$$

Table A-6 summarizes the uncertainty factors for the subchronic screening p-RfD for aluminum phosphates.

Table A-6. Uncertainty Factors for the Subchronic Screening p-RfD for Aluminum Phosphates (Multiple CASRNs)

UF	Value	Justification
UF _A	10	A UF _A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans when no cross-species dosimetric adjustment (HED calculation) is performed.
UF _D	1	A UF _D of 1 is applied because neurotoxicity and neurodevelopmental toxicity are well-documented effects of aluminum compounds in studies of rats and mice following oral exposure. Although none of the identified studies of aluminum phosphates specifically evaluated neurological endpoints, an increase in this uncertainty factor was not considered necessary, because the aluminum moiety from aluminum phosphates is expected to be less bioavailable than the aluminum moiety from other aluminum salts, which mitigates some of the concern for completeness of the database. In addition, the POD based on aluminum toxicity is more conservative than the POD based on phosphate.
UF _H	10	A UF _H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of aluminum phosphates in humans.
UF _L	1	A UF _L of 1 is applied for LOAEL-to-NOAEL extrapolation because the analogue POD is a NOAEL.
UF _S	1	A UF _S of 1 is applied because among the available subchronic and developmental studies, a developmental study is selected as the principal study, and it will be protective against subchronic systemic toxicity.
UF _C	100	Composite UF = UF _A × UF _H × UF _D × UF _L × UF _S .

HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Chronic Screening Provisional Reference Dose

The POD for the subchronic screening p-RfD is also used for derivation of the chronic screening p-RfD. This POD is further supported by co-principal studies used for the U.S. EPA screening chronic p-RfD value for aluminum phosphates, which are developmental toxicity studies of aluminum lactate in mice [Donald et al. (1989) and Golub et al. (1995) as cited in [U.S. EPA \(2006\)](#)]^{6,7}. The PPRTV assessment for aluminum provided the following summary of Donald et al. (1989) as cited in [U.S. EPA \(2006\)](#):

Groups of 16 pregnant Swiss-Webster mice were fed 25 (control group), 500 or 1000 mg Al/kg diet as aluminum lactate throughout gestation and lactation (Donald et al., 1989). The control diet was fed to pups that were selected for post-weaning neurobehavioral assessment. Reported maternal doses were 5, 100 and 200 mg Al/kg bw-day at the beginning of pregnancy and 10.5, 210 and 420 mg Al/kg bw-day near the end of lactation. No mice were exposed to lactate

⁶Donald, J.M., M.S. Golub, M.E. Gershwin and C.L. Keen. 1989. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. *Neurotoxicol. Teratol.* 11:345-351. ([as cited in U.S. EPA, 2006](#))

⁷Golub, M.S., B. Han, C.L. Keen, M.E. Gershwin and R.P. Tarara. 1995. Behavioral performance of Swiss-Webster mice exposed to excess dietary aluminum during development or during development and as adults. *Toxicol. Appl. Pharmacol.* 133:64-72. ([as cited in U.S. EPA, 2006](#))

alone. There were no treatment-related changes in maternal survival, body weight (measured on GD 0 and 16 and PDs [postnatal days] 0, 5, 10, 15 and 20), food intake, toxic signs or neurobehavior (evaluated after pups were weaned at PD 21 using the same test battery used for the pups and described below), or on litter size or postnatal growth and development in pups as assessed by body weight, toxic signs on PDs 0–55, and by crown-rump length on PDs 0 and 20.

Neurobehavioral maturation was tested in two pups per litter on PDs 8–18 with a 12-item test battery (fore- and hindlimb grasp, fore- and hindpaw placement on sticks of 2 widths, vibrissa placing, visual placing, auditory and air puff startle, eye opening and screen grasp, cling and climb). A neurobehavioral test battery was administered to six pups per litter at age 25 days (4 days postweaning) or 39 days (fore- and hindlimb grip strengths, temperature sensitivity of tail, negative geotaxis, startle reflex to air puff and auditory stimuli) or age 21 and 35 days (foot splay). The pre-weaning neurobehavioral testing showed that a significant ($p = 0.007$) number of pups in the high dose group had impaired vertical screen climb performance. The postweaning neurobehavioral assessment showed significantly ($p < 0.05$) altered performance on several tests. These included decreased forelimb grip strength at age 39 days in the low dose group, increased hindlimb grip strength at age 25 days in both low and high dose groups, increased foot splay distance at age 21 days in both low and high dose groups and at age 35 days in the low dose group, and increased forelimb grip strength at age 25 days and decreased thermal sensitivity at age 25 and 39 days in the high dose group. There were no treatment-related changes in concentrations of Al in pup liver or bone (brain tissue was not analyzed).

The study by Golub et al. (1995) as cited in [U.S. EPA \(2006\)](#) was considered an extension of the study by Donald et al. (1989) as cited in [U.S. EPA \(2006\)](#):

...pregnant female Swiss-Webster mice were exposed continuously to a semi-purified diet containing 7 (control), 500 or 1000 mg Al/kg from the time of conception, through pregnancy and lactation (Golub et al., 1995). At weaning, pups were exposed to the same Al diet as their mothers (500 or 1000 mg Al/kg) until they were 150–170 days of age or were switched to the control diet (7 mg Al/kg) for the same time period. Based on reported dosages in previous studies by the same investigators, estimated daily dosages for mice exposed to 1000 mg Al/kg diet were as follows: 200 mg/kg-day in pregnant mice, 420 mg/kg-day in lactating mice and 130 mg/kg-day in offspring (Golub et al., 1994); doses for the mice exposed to 500 mg Al/kg diet were assumed to be approximately half of that of mice fed 1000 mg Al/kg, or 100 mg/kg-day in pregnant mice, 210 mg/kg-day in lactating mice and 65 mg/kg-day in offspring. Compared to the control diet, the Al diet had no effect on dam weight, gestation length, litter size, pup weight, offspring growth or organ weights. Operant conditioning (nose poke) of offspring for delayed spatial alternation or discrimination reversal tasks was initiated at 50 days of age and continued 5 days/week for a total of 35 sessions. A neurobehavioral test battery was conducted when the offspring were 150–170 days of age (forelimb and hindlimb grip strength, temperature sensitivity, negative geotaxis, air puff and auditory startle response). Maternal and pre-weaning exposure to 500 mg Al/kg significantly affected ($p < 0.05$)

operant training in the offspring, but not performance after training in delayed spatial alternation or discrimination reversal tasks (i.e., decreased number of training sessions to achieve the training criteria). This exposure also significantly decreased forelimb and hindlimb grip strength and puff startle response ($p < 0.05$). Pre-weaning and combined pre- and post-weaning exposure to 1000 mg Al/kg-day significantly increased ($p < 0.05$) incidence of cagemate aggression at the time behavioral testing. No effects were observed on auditory startle response, temperature sensitivity or negative geotaxis in offspring. Histopathological examination of the brain and spinal cord revealed no treatment-related changes. Thus, the LOAEL for combined maternal and pre-weaning exposure on neurobehavioral effects in mice would approximate to 100 mg Al/kg-day (estimated daily maternal dosage).

The LOAEL of 100 mg Al/kg-day was selected as the POD for aluminum based on neurobehavioral effects (decreased forelimb strength, increased hindlimb grip strength, and increased hindlimb foot splay distance) in the PPRTV assessment. It was noted in the PPRTV assessment for aluminum ([U.S. EPA, 2006](#)) that the LOAEL was considered minimal because postweaning neurobehavioral effects were marginal; the toxicological significance of increased (rather than decreased) hindlimb strength is uncertain, and two of the effects (increased hindlimb strength and increased foot splay) were observed only transiently (i.e., did not persist 2 weeks after cessation of exposure).

The LOAEL of 100 mg Al/kg-day based on [U.S. EPA \(2006\)](#) is further supported by [ATSDR \(2008\)](#). In addition to the chronic p-RfD for aluminum developed by [U.S. EPA \(2006\)](#), there is a chronic oral MRL for aluminum from [ATSDR \(2008\)](#). The chronic MRL is also based on a LOAEL of 100 mg Al/kg-day for neurobehavioral effects (reductions in forelimb strength, hindlimb strength, and thermal sensitivity) in mice exposed to aluminum as aluminum lactate from conception until 24 months of age [Golub et al. (2000) as cited in [ATSDR \(2008\)](#)]. BMD modeling could not be performed for these data because the study used only one aluminum dose group. Using the LOAEL of 100 mg Al/kg-day and applying a UF_C of 300 (10-fold for UF_A , 10-fold for UF_H , and 3-fold for LOAEL-to-NOAEL uncertainty factor [UF_L]) and a MF of 0.3 (owing to the same concerns about bioavailability noted for the subchronic p-RfD) results in a chronic MRL of 1 mg Al/kg-day (equal to the value of the chronic p-RfD derived by [U.S. EPA \(2006\)](#)).

These LOAELs of 100 mg Al/kg-day based on minimal neurobehavior toxicity identified in mice exposed to aluminum for up to 24 months [Donald et al. (1989) as cited in [U.S. EPA \(2006\)](#)]; Golub et al. (2000) as cited in [ATSDR \(2008\)](#)] is consistent with the NOAEL of 26 mg Al/kg-day and LOAEL of 130 mg Al/kg-day based on similar toxicity identified in mice exposed to aluminum from gestation to postnatal day (PND) 35 [Golub and Germann (2001) as cited in [\(ATSDR, 2008\)](#)], indicating that there were likely no significant increases in severity of neurobehavioral toxicity when exposure duration increases.

Therefore, the chronic p-RfD for aluminum phosphate was derived using the NOAEL of 26 mg Al/kg-day using a UF_C of 100 based on a 10-fold UF_A and a 10-fold UF_H . A UF_D was not used because limitations in the database (e.g., lack of chronic data) were considered not to increase uncertainty in the RfD. ([U.S. EPA, 2006](#)). [Wang et al. \(2012\)](#) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are

the same as those applied to the analogue unless additional information is available. As discussed in the section on subchronic RfD derivation above, although neurological endpoints were not evaluated in studies of aluminum phosphates, an increase in UF_D was not considered necessary because the aluminum moiety from aluminum phosphates is expected to be less bioavailable than the aluminum moiety from other aluminum salts.

$$\begin{aligned} \text{Chronic Screening p-RfD} &= \text{Analogue POD} \div \text{UF}_C \\ &= 26 \text{ mg Al/kg-day} \div 100 \\ &= 3 \times 10^{-1} \text{ mg Al/kg-day} \end{aligned}$$

Table A-7 summarizes the uncertainty factors for the chronic screening p-RfD for aluminum phosphates.

Table A-7. Uncertainty Factors for the Chronic Screening p-RfD for Aluminum Phosphates (Multiple CASRNs)		
UF	Value	Justification
UF _A	10	A UF _A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans when no cross-species dosimetric adjustment (HED calculation) is performed.
UF _D	1	A UF _D of 1 is applied because neurotoxicity and neurodevelopmental toxicity are well-documented effects of aluminum compounds in studies of rats and mice following oral exposure. Although none of the identified studies of aluminum phosphates specifically evaluated neurological endpoints, an increase in this UF was not considered necessary, because the aluminum moiety from aluminum phosphates is expected to be less bioavailable than the aluminum moiety from other aluminum salts, which mitigates some of the concern for completeness of the database. In addition, the POD based on aluminum toxicity is more conservative than the POD based on phosphate.
UF _H	10	A UF _H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of aluminum phosphates in humans.
UF _L	1	A UF _L of 1 is applied for LOAEL-to-NOAEL extrapolation because the analogue POD is a NOAEL.
UF _S	1	A UF _S of 1 is applied because among the available subchronic, chronic, and developmental studies, a developmental study is selected as the principal study, and the severity of observed toxic effects doesn't appear to increase when exposure duration increases. Thus, it will be protective against chronic systemic toxicity.
UF _C	100	Composite UF = UF _A × UF _H × UF _D × UF _L × UF _S .

HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX B. DATA TABLES

Table B-1. Serum Chemistry of Male Sprague Dawley Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 28 Days^a					
Endpoint (units)	Dose Group, mg/kg-d^b				
	Control (0)	Al(OH)₃ (1,139)	KasalTM (2,436)	KasalTMII (558)	KasalTMII (2,471)
BUN (mg/dL)	17 ± 2 ^{c,d}	19 ± 2 (+12%)	22 ± 5 (+29%)	16 ± 2 (-6%)	19 ± 2 (+12%)
Creatinine (mg/dL)	0.4 ± 0.1	0.4 ± 0.1 (+0%)	0.4 ± 0.2 (+0%)	0.5 ± 0.1 (+25%)	0.7 ± 0.2 (+75%)
ALP (IU/L)	103 ± 3	102 ± 21 (-1%)	106 ± 15 (+3%)	101 ± 12 (-2%)	112 ± 14 (+9%)
ALT (IU/L)	41 ± 1	31 ± 9 (-24%)	40 ± 19 (-2%)	44 ± 16 (+7%)	45 ± 7 (+10%)
Phosphorus	10.2 ± 1.5	10 ± 1.8 (-2%)	11.7 ± 3 (+15%)	9.7 ± 1.3 (-5%)	10.9 ± 1.4 (+7%)
Sodium (mEq/L)	145 ± 2	148 ± 1* (+2%)	149 ± 2* (+3%)	149 ± 1** (+3%)	151 ± 1** (+4%)
Potassium (mEq/L)	5.3 ± 0.8	5.3 ± 0.3 (+0%)	6.1 ± 0.3 (+15%)	5.8 ± 0.8 (+9%)	5.3 ± 0.6 (+0%)
Chloride (mEq/L)	105 ± 1	106 ± 1 (+1%)	108 ± 3 (+3%)	106 ± 2 (+1%)	105 ± 2 (+0%)

^a[Hicks et al. \(1987\)](#).

^bDoses correspond to 14,470 ppm Al(OH)₃, 30,000 ppm KasalTM, 7,000 ppm KasalTMII, and 30,000 ppm KasalTMII in the diet, respectively.

^cData are means ± SD; *n* = 5 animals/treatment group.

^dValue in parentheses is % change relative to control = [(treatment mean - control mean) ÷ control mean] × 100.

*Significantly different from control by Dunnett's test (*p* < 0.05), as reported by the study authors.

**Significantly different from control by Dunnett's test (*p* < 0.01), as reported by the study authors.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; SD = standard deviation.

Table B-2. Histopathologic Findings in Male Sprague Dawley Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 28 Days^a					
Endpoint	Dose (mg/kg-d)^b				
	Control (0)	Al(OH)₃ (1,139)	KasalTM (2,436)	KasalTMII (558)	KasalTMII (2,471)
Heart					
Zenker's degeneration ²⁻³	2/5 (40%) ^c	1/5 (20%)	3/5 (60%)	2/5 (40%)	2/5 (40%)
Lymphocytic inflammation ²	1/5 (20%)	NR	NR	1/5 (20%)	1/5 (20%)
Liver					
Necrosis ¹	NR	NR	NR	1/5 (20%)	NR
Kidneys					
Cyst ⁰	NR	1/5 (20%)	NR	1/5 (20%)	NR
Cystic change ³	1/5 (20%)	NR	NR	NR	NR
Dilation ²⁻³	NR	1/5 (20%)	2/5 (40%)	1/5 (20%)	1/5 (20%)
Dilation with atrophy ²	NR	NR	NR	NR	1/5 (20%)
Glomerulonephropathy ^{d,2}	NR	NR	NR	NR	1/5 (20%)
Hyaline droplets ²⁻³	NR	3/5 (60%)	NR	2/5 (40%)	NR
Hyperplasia ²	1/5 (20%)	NR	2/5 (40%)	1/5 (20%)	1/5 (20%)
Lymphocytic inflammation ²⁻³	1/5 (20%)	NR	NR	NR	1/5 (20%)
Testes					
Calcification ²	1/5 (20%)	NR	NR	NR	NR
Atrophic degeneration ²⁻³	2/5 (40%)	NR	1/5 (20%)	NR	NR
Edema ³	NR	NR	1/5 (20%)	NR	NR

^aHicks et al. (1987).

^bDoses correspond to 14,470 ppm Al(OH)₃, 30,000 ppm KasalTM, 7,000 ppm KasalTMII, and 30,000 ppm KasalTMII in diet, respectively.

^cValues denote number of animals showing changes/total number of animals examined (% incidence). Statistical analysis results were not reported.

^dReferred to as "membranous glomerulonephropathy" in the study text.

⁰No grade applicable for endpoint.

¹Severity of endpoint graded as "slight."

²Severity of endpoint graded as "mild."

²⁻³Severity of endpoint graded as "mild to moderate."

³Severity of endpoint graded as "moderate."

NR = not reported.

Table B-3. Hematology Results in Male and Female Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a				
Endpoint	Males: Dose (mg/kg-d)^b			
	Control (0)	Kasal™ (1,803.11)	Levair® (1,909.53)	Levn Lite® (1,796.95)
Leucocytes (thousands/mm ³)	15.9 ^{c,d,e}	16 (+1%)	13.4 (-16%)	14.2 (-11%)
Erythrocytes (millions/mm ³)	8.08	7.98 (-1%)	8.05 (-0%)	8.23 (+2%)
Hemoglobin (g/100 mL)	15.9	15.7 (-1%)	15.8 (-1%)	16.2 (+2%)
Hematocrit (%)	40.5	39.6 (-2%)	40.1 (-1%)	41 (+1%)
Lymphocytes (cells/100)	86.7	84.1 (-3%)	85.8 (-1%)	83.1 (-4%)
Neutrophils (cells/100)	11.1	12.8 (+15%)	11.5 (+4%)	13.8 (+24%)
Monocytes (cells/100)	1.7	2 (+18%)	2.1 (+24%)	2.1 (+24%)
Eosinophils (cells/100)	0.5	1.1 (+120%)	0.6 (+20%)	1 (+100%)
Basophils (cells/100)	0	0 (+0%)	0 (+0%)	0 (+0%)
Endpoint	Females: Dose (mg/kg-d)			
	Control (0)	Kasal™ (2,113.79)	Levair® (1,988.42)	Levn Lite® (2,070.10)
Leucocytes (thousands/mm ³)	9.9	9.4 (-5%)	8.6 (-13%)	9.2 (-7%)
Erythrocytes (millions/mm ³)	7.52	7.59 (+1%)	7.46 (-1%)	7.77 (+3%)
Hemoglobin (g/100 mL)	15.7	15.8 (+1%)	15.6 (-1%)	15.7 (+0%)
Hematocrit (%)	37.9	39.2 (+3%)	38.3 (+1%)	39.3 (+4%)
Lymphocytes (cells/100)	85.5	86.6 (+1%)	84.3 (-1%)	87.1 (+2%)
Neutrophils (cells/100)	12.6	11.3 (-10%)	13.6 (+8%)	11.7 (-7%)
Monocytes (cells/100)	1	1.3 (+30%)	1.5 (+50%)	1 (+0%)
Eosinophils (cells/100)	0.9	0.8 (-11%)	0.6 (-33%)	0.2 (-78%)
Basophils (cells/100)	0	0 (+0%)	0 (+0%)	0 (+0%)

^aAnonymous (1972) as cited in [ECHA \(1972c\)](#); Anonymous (1972) as cited in [ECHA \(1972e\)](#); Anonymous (1972) as cited in [ECHA \(1972f\)](#).

^bDoses are equivalent to 3% of the test substances in the diets of male and female rats; measurements were not performed in low- or mid-dose groups.

^cData represent means; measurement of variance was not provided by the study authors; $n = 10$ animals/sex/dose. Statistical analysis results were not reported.

^dValue in parentheses is percent change relative to control = $[(\text{treatment mean} - \text{control mean}) \div \text{control mean}] \times 100$.

^eData from Study Day 84.

Table B-4. Serum Biochemistry and Select Urinalysis Results in Male and Female Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a

Endpoint	Males: Dose (mg/kg-d) ^b			
	Control (0)	Kasal™ (1,803.11)	Levair® (1,909.53)	Levn Lite® (1,796.95)
ALP (King-Armstrong units)	24 ^{c,d,e}	19 (-21%)	22 (-8%)	23 (-4%)
ALT (Dade units)	27	27 (+0%)	29 (+7%)	32 (+19%)
BUN (mg%)	15	15 (+0%)	NDr	14 (-7%)
Fasted glucose (mg%)	141	131 (-7%)	NDr	153 (+9%)
Urine pH	6.8	7.4 (+9%)	6.4 (-6%)	6.8 (+0%)
Urine specific gravity	1.039	1.043 (+0%)	1.049 (+1%)	1.053 (+1%)
Endpoint	Females: Dose (mg/kg-d)			
	Control (0)	Kasal™ (2,113.79)	Levair® (1,988.42)	Levn Lite® (2,070.10)
ALP (King-Armstrong units)	12	19 (+42%)	19 (+58%)	12 (+0%)
ALT (Dade units)	28	25 (-11%)	29 (+4%)	21 (-25%)
BUN (mg%)	14	16 (+14%)	NDr	14 (+0%)
Fasted glucose (mg%)	137	128 (-7%)	NDr	143 (+4%)
Urine pH	6.8	7 (+3%)	6.4 (-6%)	6.6 (-3%)
Urine specific gravity	1.036	1.03 (-1%)	1.03 (-1%)	1.032 (-0%)

^aAnonymous (1972) as cited in [ECHA \(1972c\)](#); Anonymous (1972) as cited in [ECHA \(1972e\)](#); Anonymous (1972) as cited in [ECHA \(1972f\)](#).

^bDoses are equivalent to 3% of the test substances in the diets of male and female rats; measurements were not performed in low or mid-dose groups.

^cData represent means; measurement of variance was not provided by the study authors; $n = 10$ animals/sex/dose. Statistical analysis results were not reported.

^dValue in parentheses is percent change relative to control = $[(\text{treatment mean} - \text{control mean}) \div \text{control mean}] \times 100$.

^eData from Study Day 84.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; NDr = not determined.

Table B-5. Select Organ Weights in Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a				
Endpoints	Kasal™ Males: Dose (mg/kg-d)			
	0	172.66	562.74	1,803.11
Kidney				
Absolute (g)	3.666	3.755 (+2%)	3.937 (+7%)	3.971 (+8%)
Relative to body weight (g/100g)	0.7019	0.6899 (-2%)	0.7082 (+1%)	0.7308 (+4%)
Relative to brain weight (g/g)	1.8015	1.7692 (-2%)	1.8755 (+4%)	1.8971 (+5%)
Liver				
Absolute (g)	18.14	20.853* (+15%)	19.431 (+7%)	18.462 (+2%)
Relative to body weight (g/100g)	3.479	3.8236 (+10%)	3.4787 (-0%)	3.3903 (-3%)
Relative to brain weight (g/g)	8.8872	9.8207 (+11%)	9.2459 (+4%)	8.8323 (-1%)
Endpoints	Kasal™ Females: Dose (mg/kg-d)			
	0	205.62	701.32	2,113.79
Kidney				
Absolute (g)	2.117	2.184 (+3%)	1.993 (-6%)	2.375 (+12%)
Relative to body weight (g/100g)	0.6798	0.7212 (+6%)	0.6865 (+1%)	0.7916* (+16%)
Relative to brain weight (g/g)	1.0695	1.1753 (+10%)	1.0274 (-4%)	1.2197* (+14%)
Liver				
Absolute (g)	10.064	11.633* (+16%)	9.325 (-7%)	9.485 (-6%)
Relative to body weight (g/100g)	3.2526	3.8286** (+18%)	3.2024 (-2%)	3.1562 (-3%)
Relative to brain weight (g/g)	5.0896	6.2497** (+23%)	4.8121 (-5%)	4.8732 (-4%)
Endpoints	Levair® Males: Dose (mg/kg-d)			
	0	182.57	594.65	1,909.53
Kidney				
Absolute (g)	3.666	3.699 (+1%)	3.636 (-1%)	3.886 (+6%)
Relative to body weight (g/100g)	0.7019	0.7104 (+1%)	0.6722 (-4%)	0.723 (+3%)
Relative to brain weight (g/g)	1.8015	1.8193 (+1%)	1.7239 (-4%)	1.8586 (+3%)
Endpoints	Levair® Females: Dose (mg/kg-d)			
	0	210.09	693.99	1,988.42
Kidney				
Absolute (g)	2.117	2.048 (-3%)	2.157 (+2%)	2.104 (-1%)
Relative to body weight (g/100g)	0.6798	0.6596 (-3%)	0.6984 (+3%)	0.7153 (+5%)
Relative to brain weight (g/g)	1.0695	1.0902 (+2%)	1.109 (+4%)	1.0908 (+2%)
Endpoints	Levn Lite® Males: Dose (mg/kg-d)^b			
	0	155.36	545.64	1,796.95
Kidney				
Absolute (g)	3.666 ^{c,d,e}	3.713 (+1%)	3.739 (+2%)	3.644 (-1%)
Relative to body weight (g/100g)	0.7019	0.6364 (-9%)	0.693 (-1%)	0.6812 (-3%)
Relative to brain weight (g/g)	1.8015	1.7939 (-0%)	1.8148 (+1%)	1.7462 (-3%)

Table B-5. Select Organ Weights in Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a

Kidney	Levn Lite® Females: Dose (mg/kg-d)			
	0	181.18	701.65	2,070.10
Absolute (g)	2.117	2.134 (+1%)	2.067 (-2%)	2.227 (+5%)
Relative to body weight (g/100g)	0.6798	0.6686 (-2%)	0.6688 (-2%)	0.7468* (+10%)
Relative to brain weight (g/g)	1.0695	1.1141 (+4%)	1.1259 (+5%)	1.1639 (+9%)

^aAnonymous (1972) as cited in [ECHA \(1972c\)](#); Anonymous (1972) as cited in [ECHA \(1972e\)](#); Anonymous (1972) as cited in [ECHA \(1972f\)](#).

^bDoses are equivalent to dietary concentrations of 0.3, 1.0, and 3%, respectively, for all groups.

^cData represent means; measurement of variance was not provided by the study authors; $n = 15$ animals/sex/dose in all studies.

^dValue in parentheses is percent change relative to control = $[(\text{treatment mean} - \text{control mean}) \div \text{control mean}] \times 100$.

^eThe same control data were reported for each compound.

*Statistically different from control ($p < 0.05$); statistical test not reported by the study authors.

**Statistically different from control ($p < 0.01$); statistical test not reported by the study authors.

Table B-6. Select Non-neoplastic Lesions of the Kidney in Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a				
Endpoints	Kasal™ Males: Dose (mg/kg-d)			
	0	172.66	562.74	1,803.11
Kidney				
Focal lymphoid infiltration	3/10 (30%)	NR	NR	NR
Nephrocalcinosis	NR	NR	NR	NR
Chronic nephritis	NR	NR	1/10 (10%)	NR
Tubular nephrosis	NR	NR	1/10 (10%)	NR
Focal interstitial nephritis	NR	NR	NR	2/10 (20%)
	Kasal™ Females: Dose (mg/kg-d)			
	0	205.62	701.32	2,113.79
Kidney				
Focal lymphoid infiltration	NR	1/15 (7%)	2/10 (20%)	1/10 (10%)
Nephrocalcinosis	0/10	4/15 (27%)	3/10 (30%) ^f	8/10** (80%)^f
Chronic nephritis	NR	2/15 (13%) ^f	NR	NR
Tubular nephrosis	NR	NR	NR	NR
Focal interstitial nephritis	NR	NR	NR	NR
	Levair® Males: Dose (mg/kg-d)			
	0	182.57	594.65	1,909.53
Kidney				
Focal lymphoid infiltration	3/10 (30%)	NR	NR	NR
Nephrocalcinosis	NR	NR	NR	NR
Chronic nephritis	NR	NR	NR	NR
Tubular nephrosis	NR	NR	1/10 (10%)	NR
Focal interstitial nephritis	NR	NR	NR	1/10 (10%)
	Levair® Females: Dose (mg/kg-d)			
	0	210.09	693.99	1,988.42
Kidney				
Focal lymphoid infiltration	NR	1/15 (7%) ^f	NR	NR
Nephrocalcinosis	NR	3/15 (20%)	7/10** (70%)	7/10** (70%)
Chronic nephritis	NR	1/15 (7%)	NR	NR
Tubular nephrosis	NR	NR	NR	NR
Focal interstitial nephritis	NR	NR	NR	2/10 (20%)
	Levn Lite® Males: Dose (mg/kg-d)^b			
	0	155.36	545.64	1,796.95
Kidney				
Focal lymphoid infiltration	3/10 (30%) ^{d,e}	NR	NR	1/10 (10%)
Nephrocalcinosis	NR	NR	NR	NR
Hydronephrosis	NR	NR	NR	NR

Table B-6. Select Non-neoplastic Lesions of the Kidney in Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a

Kidney	Levn Lite® Females: Dose (mg/kg-d)			
	0	181.18	701.65	2,070.10
Focal lymphoid infiltration	NR	1/15 (7%) ^f	5/10* (50%) ^f	1/10 (10%)
Nephrocalcinosis	NR	4/15 (27%)	5/10* (50%) ^f	9/10** (90%)
Hydronephrosis	NR	1/15 (7%)	NR	NR

^aAnonymous (1972) as cited in [ECHA \(1972c\)](#); Anonymous (1972) as cited in [ECHA \(1972e\)](#); Anonymous (1972) as cited in [ECHA \(1972f\)](#).

^bDoses are equivalent to dietary concentrations of 0.3, 1.0, and 3%, respectively, for all groups.

^cNephrocalcinosis referred to as “microconcretions” or “microconcentrations” in study tables; however, “nephrocalcinosis” was referenced in multiple locations in study texts.

^dValues denote number of animals showing changes/total number of animals (% incidence).

^eNumber of animals examined (*n*) = 10 for all males and for mid- and high-dose females; *n* = 15 for low-dose females.

^fSeverity scored as mild; all other incidences reported were considered minimal to slight.

*Statistically different from control (*p* < 0.05) by Fischer’s exact test (two-tailed) performed for this review. For statistical analysis, control incidences that were not reported were considered to be 0/10.

**Statistically different from control (*p* < 0.01) by Fischer’s exact test (two-tailed) performed for this review. For statistical analysis, control incidences that were not reported were considered to be 0/10.

NR = not reported; available data tables presented selected results only.

Table B-7. Body-Weight Gain and Food Consumption in Albino Rats Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a

Endpoints	Levn Lite® Males: Dose (mg/kg-d) ^b			
	0	155.36	545.64	1,796.95
Total body-weight gain (g/rat)	337 ^{c,d}	395 (+17%)	355 (+5%)	355 (+5%)
Total food consumption (g/rat)	2,296	2,318 (+1%)	2,127 (-7%)	2,194 (-4%)
Endpoints	Levn Lite® Females: Dose (mg/kg-d)			
	0	181.18	701.65	2,070.10
Total body-weight gain (g/rat)	181	162 (-10%)	157 (-13%)	148 (-18%)
Total food consumption (g/rat)	1,705	1,566 (-8%)	1,570 (-8%)	1,680 (-1%)

^aAnonymous (1972) as cited in [ECHA \(1972d\)](#).

^bDoses are equivalent to dietary concentrations of 0.3, 1.0, and 3%, respectively.

^cData represent means; measurement of variance was not provided by the study authors. *n* = 15/group for body-weight gain and *n* = 5/group for food consumption. Statistical analysis results were not reported.

^dValue in parentheses is percent change relative to control = [(treatment mean - control mean) ÷ control mean] × 100.

Table B-8. Select Histopathologic Changes in the Kidneys of Beagle Dogs Orally Administered Sodium Aluminum Phosphates in the Diet for 90 Days^a				
Endpoints	Kasal™ Males: Dose (mg/kg-d)			
	0	94.23	322.88	1,107.12
Kidneys	NR	NR	NR	NR
Congestion	NR	NR	NR	2/4 (50%)
Tubular concretions (total)	NR	NR	NR	NR
Minimal or slight	NR	NR	NR	NR
Mild	NR	NR	NR	2/4 (50%)
Moderate	NR	1/4 (25%)	NR	1/4 (25%)
Focal lymphoid infiltration (total)	NR	1/4 (25%)	NR	1/4 (25%)
Minimal or slight				
Kidneys	Kasal™ Females: Dose (mg/kg-d)			
	0	129.31	492.77	1,433.56
Kidneys	NR	NR	NR	NR
Congestion	NR	NR	NR	NR
Tubular concretions (total)	NR	NR	NR	1/4 (25%)
Minimal or slight	NR	NR	NR	NR
Mild	NR	NR	NR	NR
Moderate	NR	NR	NR	1/4 (25%)
Focal lymphoid infiltration	NR	NR	NR	NR
Kidneys	Levn Lite® Males: Dose (mg/kg-d)^b			
	0	94.55	345.21	1,038.77
Kidneys	NR ^c	NR	NR	NR
Congestion	NR	NR	NR	NR
Tubular concretions	NR	NR	NR	NR
Focal lymphoid infiltration	NR	NR	NR	NR
Kidneys	Levn Lite® Females: Dose (mg/kg-d)			
	0	118.66	511.06	1,460.76
Kidneys	NR	NR	1/4 (25%)	NR
Congestion (total)	NR	NR	1/4 (25%)	NR
Minimal or slight	NR	NR	NR	NR
Tubular concretions	NR	NR	NR	NR
Focal lymphoid infiltration	NR	NR	NR	NR

^aAnonymous (1972) as cited in [ECHA \(1972a\)](#); Anonymous (1972) as cited in [ECHA \(1972d\)](#).

^bDoses are equivalent to dietary concentrations of 0.3, 1.0, and 3%, respectively.

^cValues denote number of animals showing changes/total number of animals (% incidence). Statistical analysis results were not reported.

NR = not reported.

Table B-9. Food Consumption in Beagle Dogs Orally Exposed to Sodium Aluminum Phosphates in the Diet for 6 Months^a				
Time point	Males: Dose (mg/kg-d)^b			
	0	118	317	1,034
Week 1	230 ± 54 ^{c,d}	257 ± 67 (+12%)	239 ± 50 (+4%)	186 ± 57 (-19%)
Week 4	345 ± 64	359 ± 105 (+4%)	285 ± 62 (-17%)	303 ± 70 (-12%)
Week 8	355 ± 61	345 ± 94 (-3%)	325 ± 87 (-8%)	334 ± 77 (-6%)
Week 12	385 ± 83	373 ± 31 (-3%)	303 ± 49 (-21%)	332 ± 30 (-14%)
Week 16	405 ± 80	394 ± 99 (-3%)	319 ± 101 (-21%)	331 ± 70 (-18%)
Week 20	420 ± 88	361 ± 100 (-14%)	302 ± 73 (-28%)	328 ± 42 (-22%)
Week 24	403 ± 70	344 ± 53 (-15%)	299 ± 90 (-26%)	331 ± 74 (-18%)
Week 27	352 ± 78	322 ± 62 (-9%)	277 ± 68 (-21%)	316 ± 62 (-10%)
Time point	Females: Dose (mg/kg-d)			
	0	112	361	1,087
Week 1	220 ± 20	232 ± 24 (+5%)	241 ± 57 (+10%)	236 ± 66 (+7%)
Week 4	330 ± 37	277 ± 28* (-16%)	284 ± 46 (-14%)	273 ± 22* (-17%)
Week 8	364 ± 75	294 ± 43* (-19%)	278 ± 34* (-24%)	266 ± 18* (-27%)
Week 12	355 ± 91	303 ± 31 (-15%)	286 ± 49 (-19%)	290 ± 30 (-18%)
Week 16	334 ± 68	279 ± 44 (-16%)	261 ± 61 (-22%)	273 ± 24 (-18%)
Week 20	344 ± 83	262 ± 26* (-24%)	280 ± 35 (-19%)	277 ± 30 (-19%)
Week 24	340 ± 56	273 ± 26* (-20%)	265 ± 29* (-22%)	248 ± 19* (-27%)
Week 27	274 ± 82	232 ± 29 (-15%)	223 ± 84 (-19%)	218 ± 14 (-20%)

^aKatz et al. (1984).

^bDoses are equivalent to dietary concentrations of 0.3, 1.0, and 3%, respectively.

^cData are means ± SD; *n* = 6 animals/sex/dose; food consumption reported as g/day.

^dValue in parentheses is % change relative to control = [(treatment mean - control mean) ÷ control mean] × 100.

*Significantly different from control by Dunnett's test (*p* < 0.05), as reported by the study authors.

SD = standard deviation

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