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Provisional Peer-Reviewed Toxicity Values for

Ammonium Salts of Inorganic Phosphates:

Monoammonium Phosphate (MAP) (CASRN 7722-76-1)

Diammonium Phosphate (DAP) (CASRN 7783-28-0)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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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

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-*S*-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
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
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 document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR AMMONIUM SALTS OF INORGANIC PHOSPHATES (MONOAMMONIUM PHOSPHATE, CASRN 7722-76-1, AND DIAMMONIUM PHOSPHATE, CASRN 7783-28-0)

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 adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

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 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 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 adverse 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 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

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 its content is quite uniform across most plant and animal tissues. Orthophosphate (anionic salts of H_3PO_4) is the basic unit for all phosphates. 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 cations (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.

This document addresses the available data on the toxicity of ammonium phosphate salts (monoammonium phosphate [MAP], diammonium phosphate [DAP], and ammonium polyphosphate [APP]). Monovalent, divalent, and aluminum phosphates are not included in this assessment because they are expected to have differing toxicity, chemistry, and/or toxicokinetics than the ammonium phosphates. Specifically, ammonium phosphate salts are relatively unstable, because ammonium hydroxide is a weaker base than metal hydroxides, and ammonia can escape as a gas (Gard, 2005). The reader is referred to the PPRTV assessments for monovalent, divalent, and aluminum phosphates for assessments of these inorganic phosphate salts.

Ammonium phosphate salts are inorganic salts composed of a phosphate anion and an ammonium cation. These water-soluble salts will dissociate in aqueous environments. Phosphate is the conjugate base of phosphoric acid. Phosphoric acid is a polyprotic acid composed of three dissociable protons with different pKa constants ($pK_1 = 2.16$, $pK_2 = 7.21$, $pK_3 = 12.32$) resulting in successive deprotonation as pH increases. At very low pH values (<2) fully protonated, neutral, phosphoric acid will predominate. In aqueous environments, at pH values between 6.5 and 8.5, phosphoric acid, and mono-, di-, and triphosphates (deprotonated anions) will all exist in equilibrium depending on the specific pH of the system. An aqueous solution of phosphoric acid will therefore contain some proportion of each species. Monovalent and divalent phosphate are found in the body as inorganic anions and as functional groups on many important biomolecules. Ammonium is the conjugate acid of ammonia. Based on its pKa of 9.25, the cation will predominate at pH values below 9, with higher concentrations of the cation as the pH decreases (up to 99% at physiological pH).

Commercial inorganic phosphate salts are used in many applications. The ammonium salts of phosphoric acid addressed in this document are MAP, DAP, and APP. MAP (monovalent: $H_2PO_4^-$) and DAP (divalent: HPO_4^{2-}) are both discrete chemicals, while APP is a polymeric substance classified by Toxic Substances Control Act (TSCA) guidelines as "chemical substances of unknown or variable composition, complex reaction products and biological materials (UVCB)." Because of the variable molecular weight of APP polymers and variable water solubility, these polymeric salts will likely behave slightly differently than the discrete salts under both biological and environmental conditions. In general, as molecular weight increases and water solubility decreases, bioavailability tends to decrease. However, APP

polymers are susceptible to hydrolysis and will break down into smaller molecular weight components over time.

MAP and DAP are used as fertilizers and plant nutrients, flame retardants, in fire-extinguishers and fire-proofing agents, oral care agents, in cosmetics as buffering agents and corrosion inhibitors, and in fermentations for yeast cultures (NLM, 2019a, b, c; CIR Expert Panel, 2016; OECD, 2007a, b, e). MAP and DAP are direct food additives classified by the U.S. Food and Drug Administration (FDA) as generally recognized as safe (GRAS) (CIR Expert Panel, 2016). APP salts are generally used in flame retardants for commercial furniture, automotive fabrics, and draperies; in addition, lower molecular weight, water-soluble APP polymers are used in foods (NRC, 2000).

In general, these salts are soluble in water; however, higher molecular weight APP polymers tend to have lower water solubility. Ammonium phosphate salts will persist in natural waters. In aqueous environments, both the anion (phosphates) and cation (ammonium) are nutrients for algae, other plants, and microbes (ECHA, 2019a, b, c; CIR Expert Panel, 2016; OECD, 2007a). In air, MAP is stable; however, DAP gradually loses up to 8% NH_3 upon exposure to air (CIR Expert Panel, 2016). In aqueous systems and in soils under both aerobic and anaerobic conditions, polyphosphate salts are susceptible to hydrolysis, with reported half-lives ranging between 1 and 18 days (OECD, 2007b, d). In soil, ammonia is rapidly converted to nitrate and nitrite by *Nitrosomonas* and *Nitrobacter* bacteria, respectively (OECD, 2007a). Human exposure to ammonium phosphate salts may occur via dermal contact through their use in cosmetics, flame retardants, and fertilizers, or via ingestion through their use as food additives and plant nutrients.

The empirical formulas for and physicochemical properties of the ammonium phosphate salts are shown in Table 1.

Table 1. Identity, Molecular Weight, and Physicochemical Properties of Ammonium Phosphate Salts[a, b]

Property	MAP	DAP	APP
CASRN	7722-76-1	7783-28-0	68333-79-9
Empirical formula[c]	$NH_4H_2PO_4$	$(NH_4)_2HPO_4$	$(NH_4PO_3)_n$
Molecular weight (g/mol)	115.03	132.06	$[97]_n$;[d] molecular weights vary, may be as high as 30,000[e]
Physical state	White, tetrahedral crystals or powder	White crystals or crystalline powder	White powder;[f] liquid[d]
Melting point (°C)	190, 193.3[g]	155 (decomposes)	Varies (150−300 decomposes;[d] 141−225[f])
Density (g/cm^3 at 20°C)	1.80	1.619	Varies (1.74[f])
pH (unitless)	4.2 (0.2 M aqueous solution)	~8	Varies (6.5−7;[d] 5.0−7.0[e])
Acid dissociation constant (pKa) (unitless)[d]	pK_1 = 2.16; pK_2 = 7.21; pK_3 = 12.32 (phosphoric acid); pK_4 = 9.25 (ammonium)	pK_1 = 2.16; pK_2 = 7.21; pK_3 = 12.32 (phosphoric acid); pK_4 = 9.25 (ammonium)	Varies
Solubility in water (at 25°C)	40.4 g/100 g water	69.5 g/100 g water	Varies (miscible;[d] 4.0 g/100 g water, max solubility 10%; [e] 50% w/w, very soluble[f])

[a]Octanol-water partition coefficient, Henry's law constant, soil adsorption coefficient, atmospheric OH rate constant, and atmospheric half-life are not applicable to inorganic phosphates.
[b]NLM (2019a), NLM (2019b), and NLM (2019c), unless otherwise specified.
[c]Weiner et al. (2001).
[d]OECD (2007d).
[e]NRC (2000), chain length = 200.
[f]ECHA (2019c), chain length unspecified.
[g]CIR Expert Panel (2016).

APP = ammonium polyphosphate; DAP = diammonium phosphate; MAP = monoammonium phosphate.

A summary of available toxicity values for ammonium phosphate salts (multiple CASRNs) from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; and APP, CASRN 68333-79-9)

Source (parameter)[a, b]		Value (applicability)	Notes	Reference[c]
Noncancer				
IRIS		NV	NA	U.S. EPA (2020)
HEAST		NV	NA	U.S. EPA (2011a)
DWSHA		NV	NA	U.S. EPA (2018)
ATSDR		NV	NA	ATSDR (2020)
IPCS/WHO (MTDI)		70 mg/kg body weight (phosphates)	Group MTDI for P from all sources	IPCS (2020); WHO (1982)
CalEPA		NV	NA	CalEPA (2019); CalEPA (2020)
OSHA		NV	NA	OSHA (2018a); OSHA (2020); OSHA (2018b)
NIOSH		NV	NA	NIOSH (2018)
ACGIH		NV	NA	ACGIH (2018)
DOE (PAC)	MAP	PAC-1: 17 mg/m^3 PAC-2: 190 mg/m^3 PAC-3: 1,100 mg/m^3	PAC-1 and PAC-2 based on TEELs; PAC-3 based on rat oral LD_{50}	DOE (2018)
DOE (PAC)	DAP	PAC-1: 20 mg/m^3 PAC-2: 210 mg/m^3 PAC-3: 1,300 mg/m^3	PAC-1 and PAC-2 based on TEELs; PAC-3 based on rat oral LD_{50}	DOE (2018)
USAPHC (air-MEG)	MAP	1-h critical: 500 mg/m^3 1-h marginal: 350 mg/m^3 1-h negligible: 50 mg/m^3	Based on TEELs	U.S. APHC (2013)
USAPHC (air-MEG)	DAP	1-h critical: 250 mg/m^3 1-h marginal: 50 mg/m^3 1-h negligible: 30 mg/m^3	Based on TEELs	U.S. APHC (2013)

Table 2. Summary of Available Toxicity Values for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; and APP, CASRN 68333-79-9)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
Cancer			
IRIS	NV	NA	U.S. EPA (2020)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2019)
CalEPA	NV	NA	CalEPA (2019); CalEPA (2020)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: 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; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command; WHO = World Health Organization.
[b]Parameters: MEG = military exposure guideline; MTDI = maximum tolerable daily intake; PAC = protective action criteria, TEEL = temporary emergency exposure limit.
[c]Reference date is the publication date for the database and not the date the source was accessed.

APP = ammonium polyphosphate; DAP = diammonium phosphate; LD_{50} = median lethal dose; MAP = monoammonium phosphate; NA = not applicable; NV = not available; P = phosphorus.

Literature searches were conducted in April 2019 and updated in October 2020 and July 2021 for studies relevant to the derivation of provisional toxicity values for ammonium phosphate salts (CASRNs 7722-76-1, 7783-28-0, and 68333-79-9). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), 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), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Organisation for Economic Co-operation and

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search updates from October 2020 and July 2021.

Development (OECD) Existing Chemicals Database, OECD Screening Information Data Set (SIDS) High Production Volume (HPV) Chemicals via IPCS INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

A screening subchronic p-RfD for DAP has been derived in this assessment based on compound- (DAP-) specific data, and it is expected to be protective for MAP as well, given the physicochemical similarities between DAP and MAP (e.g., MAP possesses one less ammonium ion). However, it should not be applied to the risk assessment of APP, which is expected to have a much wider range of potential and variable structures, physicochemical properties, and ammonium content (see Table 1), and for which relevant toxicity data are not available to derive a p-RfD.

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 ammonium phosphate salts, and include all potentially relevant acute, repeated short-term, subchronic, and chronic studies as well as reproductive and developmental toxicity studies identified from the literature screening results. Principal studies used in the PPRTV assessment for derivation of provisional toxicity values are identified in bold. The phrase "statistical significance," and term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; APP, CASRN 68333-79-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses (if different), Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
Subchronic/ Chronic	91 fertilizer plant workers (30 from DAP plant, 30 from urea plant, and 31 from ammonia plant) compared with 68 controls; of the 91 total workers, 51 were presumed exposed ≤10 yr and 40 were presumed exposed >10 yr. Air samples were not taken nor were exposure levels measured.	ND	Among DAP plant workers, FVC, FEV_1, and PEFR/min were significantly reduced compared with controls. Among all fertilizer workers combined, spirometry parameters were reduced compared with controls, with greater reductions in the group with longer exposure duration (>10 yr).	NDr	NDr	Bhat and Ramaswamy (1993)	PR; due to a lack of exposure information, effect levels could not be established
Animal							
1. Oral (mg/kg-d)							
Subchronic	***Toxicity subgroup*: 5/sex, Sprague Dawley rat; DAP administered by gavage, daily for 35 d**	**0, 250, 750, 1,500 (as DAP)**	**Submucosal inflammation of the stomach, stomach thickening, horizontal banding of teeth.**	**NDr**	**250**	**Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002) (GLP-compliant study conducted according to OECD Guideline 422)**	**PS, PR by SS; considered "reliable without restriction" by ECHA (2002)**

Table 3A. Summary of Potentially Relevant Noncancer Data for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; APP, CASRN 68333-79-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses (if different), Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	10 F rabbits (strain not specified); DAP administered in drinking water (concentrations not reported) for 5-16 months	300−700 (as DAP)	Parathyroid weight increased 235%. No other toxicological parameters were assessed.	NDr	NDr	Fazekas (1954) as cited in Weiner et al. (2001)	PR, SS; effect levels could not be determined due to the limited toxicological evaluations and limited study details provided in the secondary source
Reproductive/ Developmental	*Reproductive subgroup*: 10 F, 5 M, Sprague Dawley rat; DAP administered by gavage, daily for 28 d in males and 53 d in females (2 wk prior to mating, through mating and gestation, until LD 4)	0, 250, 750, 1,500 (as DAP)	No reproductive or developmental effects reported at highest dose.	1,500 (reproductive/ developmental)	NDr	Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002) (GLP-compliant study conducted according to OECD Guideline 422)	PR by SS; considered "reliable without restriction" by ECHA (2002)

Table 3A. Summary of Potentially Relevant Noncancer Data for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; APP, CASRN 68333-79-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses (if different), Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
2. Inhalation (mg/m^3)							
ND							

[a]Duration 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).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects.
[c]Notes: PR = peer reviewed; PS = principal study; SS = available only as reported in secondary source.

ADD = adjusted daily dose; APP = ammonium polyphosphate; DAP = diammonium phosphate; F = female(s); FEV_1 = forced expiratory volume of 1 second; FVC = forced vital capacity; GLP = Good Laboratory Practice; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); MAP = monoammonium phosphate; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; OECD = Organisation for Economic Co-operation and Development; PEFR = peak expiratory flow rate.

Table 3B. Summary of Potentially Relevant Cancer Data for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; APP, CASRN 68333-79-9)

Category	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry	Critical Effects	Reference (comments)
Human				
1. Oral (mg/kg-d)				
ND				
2. Inhalation (mg/m^3)				
ND				
Animal				
1. Oral (mg/kg-d)				
ND				
2. Inhalation (mg/m^3)				
ND				

APP = ammonium polyphosphate; DAP = diammonium phosphate; MAP = monoammonium phosphate; ND = no data.

2.1. HUMAN STUDIES

2.1.1. Occupational Studies

Bhat and Ramaswamy (1993)

In a published occupational health study, 91 workers in fertilizer plants in India were evaluated for respiratory function and compared with 68 controls matched for age, sex, body surface area, and socioeconomic status (Bhat and Ramaswamy, 1993). Of the 91 workers, 30 worked at a DAP plant, 30 worked at a urea plant, and 31 worked at an ammonia plant. Smokers were excluded from the study due to potential for confounding. No air samples were taken, and DAP exposure concentrations were not reported. Spirometry parameters (forced vital capacity [FVC], forced expiratory volume of 1 second [FEV_1], and peak expiratory flow rate [PEFR]/minute) were evaluated using a portable spirometer. The study authors did not report the timing of spirometry measurements (e.g., before or after shift; before, during, or after a work week) or any further information on the selected controls.

Presumed exposure to DAP had a greater association with respiratory parameters than presumed exposure to urea or ammonia (Bhat and Ramaswamy, 1993). As reported in Table B-1, significant reductions in FVC, FEV_1, and PEFR/minute were observed in workers at the DAP plant. Workers in all plants combined (not stratified by fertilizer type) were categorized by duration of employment: workers exposed (presumed) 0−10 years (51), workers exposed (presumed) for >10 years (40), and nonworker controls (68). Significant decreases in FEV_1 and PEFR/minute were observed in workers exposed (presumed) 0−10 years compared to controls. All parameters were significantly decreased in workers exposed (presumed) >10 years. Due to a lack of any exposure information, these data are inadequate to establish effect levels.

Ruhe and Ehrenberg (1985)

NIOSH conducted an occupational health survey of 43 workers at an electric power facility construction site. At the site, insulation containing fiberglass, long-chain hydrocarbons, and ammonium phosphate was being cut (with a saw), resulting in airborne particles. Personal monitoring samples were collected and analyzed for formaldehyde and particulate but not for ammonium phosphate. Workers were asked to report irritation and "constitutional" symptoms occurring during the 24 hours and the 7 days prior to the site visit. Common symptoms reported by the workers were chest congestion, nasal irritation, and throat irritation. No relationship was found between exposure to the insulation particulate and prevalence of any symptom.

2.1.2. Other Human Studies

Fire extinguishers contain large, varying amounts of MAP in powder form (34−40% in some reports). Intentional inhalation and/or ingestion of fire extinguishing powder (during suicide attempts) has reportedly caused electrolyte imbalance and metabolic acidosis in numerous case studies [Becker et al. (2018) (published in German with English abstract), Doyon and McGrath (2003) (abstract only), Lee et al. (2016), Lin et al. (2009), Senthilkumaran et al. (2012)]. MAP doses were not estimated for these cases; however, serum phosphate levels in the patients were reported, ranging between 9.8 and 30.6 mg/dL (normal range is 2.3−4.5 mg/dL) [Doyon and McGrath (2003) (abstract only), Lee et al. (2016), Lin et al. (2009), Senthilkumaran et al. (2012)]. Effects reported in the patients included respiratory tract irritation, hyperphosphatemia, hypocalcemia, metabolic acidosis, delayed aspiration pneumonia, acute kidney failure, and cardiac arrest. A case study (Blumenthal and Hänert-Van der Zee, 2018) detailing autopsy results after a suicide reported a number of findings consistent with injury due to fire extinguisher pressure (e.g., ethmoid fracture, esophageal rupture, alveolar distension and rupture) as well as histology changes that may or may not be related to these injuries (pulmonary

edema, vascular congestion, crystalline lattice in some alveoli). Effects attributable to ammonium phosphate exposure could not be discerned in this case.

Two studies conducted in the 1930s evaluated the use of ammonium phosphate salts (not further described) as urinary acidifiers, apparently to enhance the action of "urinary antiseptics" such as hexamine. Scott (1931) administered 20 g ammonium phosphate in solution to five volunteers 4 times/day, alternating 2 days of administration and 2 days off for 20 days (10 days of treatment). Urine samples collected over the course of the study showed that urine tended to be at lower pH when administered DAP when compared with samples collected on days that DAP was not administered; no other endpoints were evaluated. Alstead (1936) administered "acid ammonium phosphate" in doses of 2.1−6 g to 34 hospital patient volunteers 3 or 4 times/day for an unspecified duration and compared the patients' urinary pH levels with those seen in patients receiving sodium phosphate. The results showed decreased urinary pH with administration of ammonium phosphate, compared with sodium phosphate.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

Subchronic Studies

Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)

In an unpublished, Good Laboratory Practice (GLP)-compliant, OECD 422 guideline study cited in OECD (2007b), OECD (2007f), and ECHA (2002), Sprague Dawley rats (5/sex per *toxicity subgroup*; 10 females and 5 males per *reproductive subgroup*) were administered 0, 250, 750, or 1,500 mg DAP/kg-day [purity >87% as reported in OECD (2007b) and OECD (2007c)] via gavage in water for 35 days (toxicity subgroup) or through Lactation Day (LD) 4 in females (28 and 53 days of exposure for parental males and females, respectively) of the reproductive subgroup [Huntingdon (2002) as cited in OECD (2007b)]. Doses were analytically verified by spectrophotometry. The source, nature, and composition of the animals' diet, including the calcium and baseline phosphate contents, were not reported. Mortality, clinical signs, body weight, and food consumption were monitored. In the toxicity subgroup, blood was collected during Week 5 for determination of hematology (comprehensive endpoints including clotting parameters) and clinical chemistry (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transferase [GGT], total bilirubin, albumin, total protein, urea, creatinine, glucose, total cholesterol, and electrolytes) for the toxicity, but not the reproductive, subgroup. Functional operational battery (FOB) endpoints (approach response, touch response, auditory startle reflex, tail pinch response, forelimb and hindlimb grip strength, and motor activity) were evaluated after 4 weeks. The following tissues from the toxicity subgroup were weighed: adrenals, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, prostate, seminal vesicles, spleen, testes, thymus, thyroids with parathyroid, uterus with cervix, and vagina. Although organ weights measured in the reproductive subgroup were not specified, the test guideline followed in the study (OECD 422) (OECD, 1996) indicates that organs weighed for reproductive effects include gonads (testes and ovaries), accessory sex organs (uterus and cervix, epididymides, prostate, seminal vesicles plus coagulating glands), and vagina. In the toxicology subgroup, organs fixed for histological analysis included any with observed abnormalities, as well as the adrenals, aorta, brain, caecum, colon, duodenum, epididymides, eyes, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes, mammary area, esophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary glands, sciatic nerves, seminal vesicles, skin, spinal cord, spleen, sternum (bone marrow), stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, and vagina. In the reproductive subgroup, organs fixed for histological analysis included those with abnormalities, as well as reproductive organs (not

specified, but likely included gonads and accessory sex organs based on OECD 422). Reproductive parameters (mating, gestation, and parturition parameters, including: precoital interval, mating performance, and fertility; gestation length and gestation index; litter size; and offspring survival indices) were assessed, and offspring were evaluated (litter size, offspring survival indices, sex ratio, offspring body weight, and gross pathology) through Postnatal Day (PND) 4.

Statistical tests were conducted using Fisher's exact test for categorical data and Bartlett's test for continuous data comparisons to control, incorporating multiple comparisons where needed. In the instance of a positive Bartlett's test, a Behrens's Fisher test was used for pairwise comparisons; otherwise, a Dunnett's test was used.

One female in the 1,500 mg DAP/kg-day toxicity subgroup died during the study (time point not reported); ECHA (2002) noted that findings in this animal were consistent with dosing error.[2] Dose-dependent increased incidences of the clinical signs of postdosing salivation and reddening of the extremities were noted starting at 250 mg DAP/kg-day. Decreased body-weight gain (78% of control value) was reported in males, but not females, of the 1,500-mg DAP/kg-day toxicity subgroup. Food consumption was marginally suppressed in males of the 1,500-mg DAP/kg-day group only. In the reproductive subgroup, an initial decrease in body-weight gain was noted in females during the 1st week of gestation, but body weights recovered to control levels after the week and remained normal through PND 4. No neurological effects were observed during the FOB. The only hematological finding was reduced activated partial thromboplastin time in males, but not females, administered 750 or 1,500 mg DAP/kg-day [26 and 24% less than controls, respectively; statistically significant changes reported here and below based on ECHA (2002) and OECD (2007b) unless otherwise noted]. Clinical chemistry alterations in males were increased ALP (32 and 31% higher than controls at 750 and 1,500 mg DAP/kg-day, respectively), decreased glucose (21% less than control) and phosphorus (18% less than control) at 1,500 mg/kg-day, decreased total protein (7 and 9% less than control at 750 and 1,500 mg DAP/kg-day, respectively), and a 17% increase in albumin:globulin (A/G) ratio at 1,500 mg DAP/kg-day. Clinical chemistry alterations in females were decreased phosphorus levels (19% less than controls) and a nonsignificant increase in ALP (22%) at 1,500 mg DAP/kg-day. Relative liver and kidney weights were increased (quantitative data not reported) in females at 1,500 mg DAP/kg-day; no organ-weight changes were noted in males. Both sexes exhibited horizontal banding on the incisors of teeth in the 750 and 1,500-mg DAP/kg-day dose groups; histological examination showed that this was limited to the enamel and likely reflected direct effects on tooth mineralization. Thickening of the stomach was also noted upon gross examination in both sexes at doses ≥750 mg DAP/kg-day. In the toxicity subgroup, histological evidence of submucosal inflammation in the stomach was noted in 0/5, 3/5, 4/5, and 2/5 males and 0/5, 2/5, 4/5, and 4/5 females at doses of 0, 250, 750, and 1,500 mg DAP/kg-day, respectively (see also Table B-2). The severity of these lesions was reported to be only minimal or slight in all cases. Incidences were statistically significant in females at doses ≥750 mg DAP/kg-day and males at 750 mg DAP/kg-day. Because the available data did not suggest sex differences in the inflammation, the incidences in males and females were combined for this review to increase statistical power. When incidences for males and females in the toxicity subgroup were combined (0/10, 5/10, 8/10, 6/10), the incidences at all doses were significantly increased relative to controls ($p \leq 0.05$ by Fisher's exact test performed

[2]Despite the death, histopathology incidence data provided in OECD (2007b), OECD (2007f), and ECHA (2002) are reported for five females in this group, suggesting that the animal that died prematurely was included in the results.

for this review) (see Table B-2). Stomachs were not examined microscopically in the reproductive subgroup. No other histological findings were reported. No effects were reported on mating or fertility, and no effects on offspring were observed through PND 4 in the reproductive subgroup.

A reproductive/developmental no-observed-adverse-effect level (NOAEL) of 1,500 mg DAP/kg-day (the highest dose tested) was identified by ECHA (2002) and OECD (2007b); a lowest-observed-adverse-effect level (LOAEL) could not be determined. OECD (2007f) identified a systemic NOAEL of 250 mg DAP/kg-day and a LOAEL of 750 mg DAP/kg-day for this study based on degenerative changes in the stomach,[3] noting that the incidences of histologic changes in the stomach were not statistically significant in males or females at the low dose. ECHA (2002) identified the same effect levels, but based the LOAEL on dental banding, which was of questionable biological relevance; ECHA (2002) attributed the stomach effects to local irritation rather than systemic toxicity and did not consider this local effect as a potential basis for the LOAEL. Based on the significant increase in the incidence of stomach lesions in male and female rats (combined) at all doses in the study, the LOAEL determined for this review is 250 mg DAP/kg-day; a NOAEL could not be determined. As noted above, the calcium and baseline phosphate contents of the feed administered in this study were not reported. Although the ratio of calcium to phosphate can be an important determinant of phosphate toxicity in mammals, there were no indications of excess phosphate intake (e.g., laxative or renal effects) in the animals, and inadequate calcium intake is not considered a plausible cause of stomach inflammation in the current study with ammonium phosphate. The critical effects observed in the principal study (contact irritant effects in the stomach) might be attributable to the ammonium anion, since damage to the gastrointestinal mucosa has been observed in rats after oral exposure to other ammonium compounds (ammonium hydroxide, ammonium chloride, and ammonia) [reviewed by ATSDR (2004)]. Gavage bolus dosing also would have delivered a high, instantaneous local exposure to the stomach, which may have contributed to the observed local effects. Local stomach irritation (although more extensive, including submucosal inflammation, epithelial hyperplasia, acantholysis, increased numbers of mucous secreting cells) was also observed at all (identical) doses in another GLP-compliant, OECD 422 guideline study conducted also by gavage with granular triple superphosphate (GTSP; composed of calcium and phosphate) in rats. The effects were attributed to irritation along with the low pH (2−3) of that test substance (OECD, 2007c). Finally, it is possible that dental bands and/or increased serum ALP observed in Huntingdon (2002) [as cited in OECD (2007b), OECD (2007f), and ECHA (2002)] could be related to higher phosphate intake, but these effects occurred at higher doses (≥750 mg/kg-day) than the stomach inflammation.

Chronic Studies

Fazekas (1954) as cited in Weiner et al. (2001)

In a study published in German and summarized in a review by Weiner et al. (2001), 10 female rabbits (strain not specified) were exposed to DAP in drinking water for 5−16 months. The review by Weiner et al. (2001) reported the doses as 300−700 mg/kg-day and indicated that parathyroid gland weight was the only toxicological endpoint assessed in the study. According to Weiner et al. (2001), the mean parathyroid weight was increased by 235% compared to controls. No further information was provided in the secondary source. Effect levels could not be

[3]The OECD (2007f) study for phosphates also reported degenerative changes in the kidneys as a basis for the LOAEL; however, no evidence of kidney effects was reported in the OECD (2007b) robust summary or in the ECHA (2002) summary of the study.

determined because of the limited toxicological evaluations and limited study details provided in the secondary source.

Reproductive/Developmental Studies

The study by Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002) included a screening analysis for reproductive and developmental effects (reproductive subgroup). Details and results are described above in the "Subchronic Studies" section. As reported there, a reproductive/developmental NOAEL of 1,500 mg DAP/kg-day (the highest dose tested) is identified for this study.

2.2.2. Inhalation Exposures

No repeated-dose studies of animals exposed to MAP, DAP, or APP 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 DAP and MAP.

2.3.1. Genotoxicity

Data pertaining to the genotoxic activity of ammonium phosphate salts are very limited, and the only studies available are unpublished studies reported in secondary sources, although OECD and ECHA peer reviewed these primary studies. DAP was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* with or without metabolic activation [Wagner and Klug (2001) as cited in OECD (2007b) and ECHA (2001a)] and did not increase chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells in vitro, with or without metabolic activation [Gudi and Brown (2001) as cited in OECD (2007b) and ECHA (2001b)]. MAP was not mutagenic to mouse L5178Y/TK+/− lymphoma cells with or without metabolic activation (ECHA, 2010a).

Table 4. Summary of Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; and APP, CASRN 68333-79-9) Genotoxicity

Endpoint (substance)	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutagenicity (DAP)	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, *Escherichia coli* WP2 *urvA*	Experiment 1: 2.5, 7.5, 25, 75, 200, 600, 1,800, 5,000 µg DAP/plate; Experiment 2: 50, 150, 500, 1,500, 5,000 µg DAP/plate	−	−	Plate incorporation assay. Precipitation noted at ≥1,800 µg DAP/plate in Experiment 1 and at 5,000 µg DAP/plate in Experiment 2, with or without metabolic activation. No cytotoxicity was observed. Positive controls for each strain produced expected results.	Wagner and Klug (2001) as cited in OECD (2007b) and ECHA (2001a)
Genotoxicity studies in mammalian cells—in vitro						
Mutagenicity (MAP)	L5178Y/TK+/− mouse lymphoma cells	Experiment 1 (3-h exposure): 0.003, 0.03, 0.1, 0.25, 0.5, 1, 1.4, 2 µg MAP/mL (without activation) or 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 12 µg MAP/mL (with activation); Experiment 2: 0.01, 0.03, 0.1, 0.25, 0.5, 1, 1.4, 1.8 µg MAP/mL (without activation, 24-h exposure) or 0.01, 0.1, 1, 10, 12, 14, 16, 17 µg MAP/mL (with activation, 3-h exposure)	−	−	No cytotoxicity or precipitation were observed. Positive controls produced expected results.	Anonymous (2010) as cited in ECHA (2010a)
Clastogenicity [CA] (DAP)	CHO cells	165, 330, 660 µg DAP/mL (without activation, exposure for 4 or 20 h); 330, 660, 1,320 µg DAP/mL (with activation, exposure for 4 h)	−	−	Precipitate was observed at 1,320 µg DAP/mL. Cytotoxicity was seen at 660 µg DAP/mL in tests performed without activation (4 or 20 h). Positive controls provided expected results.	Gudi and Brown (2001) as cited in OECD (2007b) and ECHA (2001b)

[a]+ = positive, (+) = weak positive, − = negative, ± = equivocal.

APP = ammonium polyphosphate; CA = chromosomal aberration; CHO = Chinese hamster ovary; DAP = diammonium phosphate; MAP = monoammonium phosphate.

2.3.2. Other Animal Studies

Ammonium phosphate salts exhibit low acute lethal potential based on unpublished data in peer-reviewed secondary sources. Unpublished acute lethality limit tests performed according to OECD Guideline 405 (OECD, 2021) were reported in OECD (2007a), OECD (2007b), and OECD (2007d). The oral median lethal dose (LD_{50}) values determined in rats were >2,000 mg/kg for MAP, DAP, and APP, and no clinical signs or body-weight changes were reported [Merkel (2000) as cited in OECD (2007a), OECD (2007b), and OECD (2007d)]. In a review, Weiner et al. (2001) reported the following oral LD_{50} values for rats: >1,000 and 5,750 mg/kg for MAP; >1,000, 6,500, and >25,100 mg/kg for DAP; and >2,000 mg/kg for APP, as well as the following dermal LD_{50} values for rabbits: >7,940 mg/kg (MAP), >10,000 mg/kg (DAP), and >2,000 mg/kg (APP), citing unpublished studies by Stauffer, Solutia, and Albright and Wilson. A 4-hour inhalation median lethal concentration (LC_{50}) value of >5.09 mg/L for APP was noted in the same review (Weiner et al., 2001). No details of study design or results, and no information on clinical signs, body-weight changes, or necropsy findings were reported by Weiner et al. (2001).

In an acute lethality study of the ammonium phosphate fire retardant PHOS-CHEK 259-F (>90% DAP and <5% guar gum according to material safety data sheet; other ingredients not reported) (ICL, 2015) in male and female rats, gavage doses of 2,000, 2,520, 3,175, and 4,000 mg/kg resulted in the following mortality incidences: 9/10, 1/10, 8/10, and 7/10. However, no LD_{50} values could be estimated from these data (Monsanto, 1992). Clinical signs of sedation, ataxia, and ptosis, as well as gastrointestinal distress, were observed, and necropsy showed gastrointestinal distension and darkened stomachs. Monsanto (1992) estimated an LD_{50} of >5,000 mg/kg in a rabbit dermal lethality study of PHOS-CHEK 259-F. In the dermal study, body-weight loss was noted in 7/10 rabbits, erythema and edema were observed, and at necropsy, there was a loss of body fat (10/10 rabbits), as well as hepatic, renal, and splenic abnormalities; in addition, enlarged gall bladder was observed in 2/5 males. Other LD_{50} values for ammonium phosphate fire retardants were reported; however, these products (PHOS-CHEK XAF and PHOS-CHEK 75-D) are of low or unknown ammonium phosphate composition. No composition information was located for PHOS-CHEK XAF, while PHOS-CHEK 75-D is reportedly composed of >65% diammonium sulfate, >5% DAP, and >15% MAP (ICL, 2006); thus, these LD_{50} values, all higher than those reported above, are not reported here.

Following studies showing that other phosphates exhibited a cariostatic effect, DAP was tested for prevention of dental caries (cavities) in white rats (sex and strain not reported) (McClure, 1964). DAP administered in the diet at concentrations between 0.55 and 3.33% for 60−90 days reduced the incidence of rats with caries, the numbers of carious teeth per rat, and the caries severity score per rat. No other toxicological endpoints were evaluated. In a study reported only in abstract form, Ivy et al. (1974) observed lower body weight and percent femur ash in rats administered DAP in the diet (at levels equivalent to 0.5, 0.7, or 0.9% phosphorus) for 70 days when compared with rats exposed to sodium phosphate, which provided equivalent concentrations of phosphorus. Finally, turkeys given DAP in the diet for 8 weeks exhibited similar tibia breaking strength when compared with those administered other dietary phosphate sources with varying fluorine content (Struwe and Sullivan, 1975).

Clawson and Armstrong (1981) administered APP (replacing 0, 50, or 100% phosphorus in diet, in place of defluorinated rock phosphate) to groups of seven rats (three males and four females) for 4 weeks and observed increased food intake and weight gain, although the changes were not monotonic with exposure. The study authors did not evaluate other toxicological endpoints. Other studies with APP are limited to evaluations of growth in agricultural species, in

which APP was tested as a source of nutritional nitrogen and phosphorus. Administration of APP did not affect growth or feed consumption in pigs when compared with other supplements, such as dicalcium phosphate (Tunmire et al., 1983; Clawson and Armstrong, 1981; Kornegay, 1972). In cows, Colenbrander et al. (1971) found that addition of APP in the diet for 8 weeks increased growth and plasma phosphorus while decreasing urinary pH. In sheep and lambs, addition of APP to the diet or in drinking water for 1−13 weeks likewise resulted in higher body-weight gains, blood phosphorus concentrations, and retention of phosphorus (Koolivand et al., 2019; Hemingway and Fishwick, 1975; Fishwick and Hemingway, 1974). In 3-week experiments in chickens, supplementation with APP in the drinking water resulted in increased food consumption, growth, phosphorus intake, and phosphorus concentration in tibia ash compared with controls (Damron and Flunker, 1990; Jensen and Edwards, 1980).

The ammonium phosphates (APP, MAP, and DAP), as well as PHOS-CHEK 259-F, were considered either nonirritating or slightly to mildly irritating when applied to the skin or eyes in tests conducted in rabbits (Weiner et al., 2001; Monsanto, 1992; Aoyama, 1975). DAP was also determined to be nonsensitizing by the dermal route (ECHA, 2010b).

2.3.3. Metabolism/Toxicokinetic Studies

Gastrointestinal absorption of phosphate from DAP has been studied in dogs. Summerill and Lee (1985) administered DAP (15 mmol in two doses 2 hours apart) by stomach tube to eight mongrel dogs and measured plasma and urinary phosphate levels for up to 4 hours. Plasma phosphate levels were increased in exposed dogs (1.63 and 1.91 mmol/L at 1.5−2 and 3.5−4 hours, respectively, compared with 0.88 and 0.94 mmol/L in four control animals), while creatinine clearance was unchanged. The study authors estimated phosphate absorption to be about 50%, based on plasma phosphate levels obtained in the 4 hours after the first dose and the assumption that phosphate was distributed evenly throughout the extracellular fluid.

2.3.4. Mode-of-Action/Mechanistic Studies

An in vitro study used neuro-derived cell lines (PC12 pheochromocytoma and B35 neuroblastoma) to evaluate the neurotoxic potential of several fire retardants, including APP (Hendriks et al., 2014). Exposure to concentrations up to 1,300 μM APP was not cytotoxic to PC12 cells, but cytotoxicity was observed in B35 cells at concentrations of at least 13 μM. Hendriks et al. (2014) reported that APP concentrations of 7 or 700 μM increased reactive oxygen species production in B35 and PC12 cells but noted that the results may have been confounded by interaction of the compound with the fluorescent dye used in the assay. APP did not affect basal levels of intracellular calcium in either cell type but did inhibit the depolarization-evoked rise in intracellular calcium concentration. Finally, APP reportedly exhibited antagonistic effects on human nicotinic acetylcholine receptor at ≥1,300 μM (Hendriks et al., 2014). The study authors concluded that APP exhibited low neurotoxic potential based on the in vitro results.

A number of other in vitro studies were identified in which ammonium phosphate was used as a phosphate source to evaluate mechanisms of changing membrane porosity during mitochondrial swelling (Sitaramam and Rao, 1992; Stoner and Sirak, 1978; Hommes et al., 1975; Lundberg, 1975; Chateaubodeau et al., 1974; Stoner and Sirak, 1971). The relevance of these studies to mechanisms of toxicity for ammonium phosphate compounds is uncertain.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

No adequate repeated-dose oral toxicity studies were identified for MAP or APP. The database of oral toxicity studies in animals exposed to DAP is limited to a German-language chronic study in rabbits evaluating only parathyroid weight [Fazekas (1954) as cited in Weiner et al. (2001)] and a combined 35-day repeated-dose toxicity and 28/53 days (males/females) reproductive/developmental screening study in rats [Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)]. The study by Fazekas (1954) as cited in Weiner et al. (2001) is not adequate for deriving a provisional reference dose (p-RfD). The study was published in German with only a brief summary reported in the review by Weiner et al. (2001); furthermore, the only endpoint evaluated was parathyroid gland weight, so effect levels could not be determined. The study by Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002) was GLP-compliant, conducted according to OECD Test Guideline 422 (OECD, 1996), and evaluated numerous systemic (including neurological), reproductive, and developmental endpoints. This study was not published and is available as reported in secondary sources; therefore, this study was not considered suitable for deriving a p-RfD. However, the study was reviewed by both OECD HPV and ECHA, both of which are peer-review processes. The study appears to have been well conducted, was considered "reliable without restriction" by ECHA, and provides sufficient data to develop a screening-level subchronic p-RfD value for DAP (see Appendix A). Human and animal data are insufficient to derive a chronic p-RfD for ammonium phosphate salts, as discussed below.

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

Human and animal data are insufficient to derive subchronic or chronic provisional reference concentrations (p-RfCs) for ammonium phosphate salts. The only available repeated-exposure information consists of a published occupational health study by Bhat and Ramaswamy (1993) and a NIOSH Human Hazard Evaluation (Ruhe and Ehrenberg, 1985); neither study evaluated ammonium phosphate exposure levels, precluding identification of effect levels.

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 5 presents a summary of noncancer provisional references values.

Table 5. Summary of Noncancer Reference Values for DAP (CASRN 7783-28-0) and MAP (CASRN 7722-76-1)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Screening subchronic p-RfD (mg DAP/kg-d) (see Appendix A)	Rat/both	Submucosal inflammation in stomach	9×10^{-2}	$BMDL_{10}$	27.7	300	Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BMD = benchmark dose; BMDL = 95% benchmark dose lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; DAP = diammonium phosphate; HED = human equivalent dose; MAP = monoammonium phosphate; NDr = not determined; 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 MAP, DAP, and APP. No human or animal studies evaluating cancer endpoints are available for any of the chemicals. Limited in vitro genotoxicity assays of DAP and MAP available in peer-reviewed secondary sources (see Table 4) 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 MAP, DAP, and APP is *"Inadequate Information to Assess Carcinogenic Potential"* (for both oral and inhalation routes of exposure).

Table 6. Cancer WOE Descriptor for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; and APP, CASRN 68333-79-9)

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.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no animal carcinogenicity studies identified to support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no animal carcinogenicity studies identified to support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any information on carcinogenicity of MAP, DAP, and APP.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

APP = ammonium polyphosphate; DAP = diammonium phosphate; MAP = monoammonium phosphate; 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 not supported (see Table 7).

Table 7. Summary of Cancer Risk Estimates for Ammonium Phosphate Salts (MAP, CASRN 7722-76-1; DAP, CASRN 7783-28-0; and APP, CASRN 68333-79-9)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

APP = ammonium polyphosphate; DAP = diammonium phosphate; MAP = monoammonium phosphate; NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional reference doses (p-RfDs) for any of the ammonium phosphate salts. However, some information is available for diammonium phosphate (DAP), 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 may be more uncertainty associated with the derivation of 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 CPHEA.

DERIVATION OF SCREENING PROVISIONAL REFERENCE DOSES

As discussed in the main body of the report, the only available oral study with adequate information to derive effect levels [Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)] was unpublished and available as reported in a secondary source. However, this Good Laboratory Practice (GLP)- and Organisation for Economic Co-operation and Development (OECD) guideline-compliant study appears to have been well conducted, was peer reviewed by the European Chemicals Agency (ECHA) and OECD and provides dose-response information suitable for deriving a screening-level provisional toxicity value for DAP.

A lowest-observed-adverse-effect level (LOAEL) of 250 mg DAP/kg-day (the lowest dose tested) was identified for the study by Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002) based on increased incidence of stomach submucosal inflammation in both sexes at all doses. Benchmark dose (BMD) modeling on the stomach inflammation data (see Table B-2) was completed using the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS, Version 3.1.1). Combined incidences in male and female rats (higher *n* vs. sex-specific) were modeled to reduce uncertainty around benchmark dose lower confidence limit (BMDL) estimates, as consistent with Agency guidance.[4] Results of BMD modeling are summarized in Appendix C. Despite a flat dose-response, model results yielded satisfactory fit of the data for several models after the high dose was dropped, with BMD_{10} and $BMDL_{10}$ estimates of 44.3 and 27.7 mg DAP/kg-day, respectively. A $BMDL_{10}$ of 27.7 mg/kg-day was therefore selected as the point of departure (POD). Confidence in this value is increased by the recognition that it is virtually identical to that derived from an alternative approach using the animal LOAEL of 250 mg/kg-day from the critical study as POD and applying a LOAEL-to-no-observed-adverse-effect level (NOAEL) uncertainty factor (UF_L) of 10.

Derivation of Screening Subchronic Provisional Reference Dose

U.S. EPA endorses a hierarchy of approaches to derive human equivalent doses (HEDs) from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Another approach may include using chemical-specific

[4]Section 2.1.6 (Combining Data for a BMD Calculation) of *Benchmark Dose Technical Guidance* (U.S. EPA, 2012).

information, including what is known about the toxicokinetics and toxicodynamics of the chemical, to derive chemical-specific adjustments. In the absence of chemical-specific information to derive human equivalent oral exposures, U.S. EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an oral reference dose (RfD) under certain exposure conditions (U.S. EPA, 2011b). More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not typically for portal-of-entry effects. Because the selected critical effect is stomach submucosal inflammation (portal-of-entry effect) in rats, the use of $BW^{3/4}$ scaling is not appropriate in this case.

A screening subchronic p-RfD of 9×10^{-2} mg DAP/kg-day is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 10, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 3 to the selected POD of 27.7 mg DAP/kg-day ($BMDL_{10}$) for submucosal inflammation in stomach of rats exposed to DAP, as follows:

Screening Subchronic p-RfD	=	$BMDL_{10} \div UF_C$
	=	27.7 mg DAP/kg-day ÷ 300
	=	**9×10^{-2} mg DAP/kg-day**

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfD for DAP. The screening subchronic p-RfD for DAP is expected to be protective for monoammonium phosphate (MAP) also, given the physicochemical similarities between DAP and MAP (e.g., MAP possesses one less ammonium ion). However, it should not be applied to the risk assessment of ammonium polyphosphate, which is anticipated to have a much wider range of potential and variable structures, physicochemical properties, and ammonium content (see Table 1), and for which relevant toxicity data are not available to derive a p-RfD.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfD for DAP (CASRN 7783-28-0) and MAP (CASRN 7722-76-1)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty in extrapolating from animals to humans for oral portal-of-entry effects of DAP.
UF_D	3	A UF_D of 3 is applied to account for deficiencies and uncertainties in the database. The oral database for ammonium phosphate salts includes secondary, peer-reviewed accounts of acute lethality studies in rats, a well-conducted, GLP- and OECD guideline-compliant 35-d combined repeated-dose and 28/53 (M/F)-d reproductive/developmental screening toxicity study in rats (critical study), a chronic study in rabbits evaluating only parathyroid gland weight, and negative genotoxicity studies. In the critical study, no reproductive, developmental, or neurobehavioral effects were observed up to the highest dose tested (1,500 mg/kg-d), which exceeded the limit dose, in either the toxicity or reproductive arm of the critical study. Local toxicity at the site of administration is considered the critical effect with DAP. Therefore, the UF_D can be reduced from 10 to 3.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility to portal-of-entry effects from oral exposure to DAP.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMDL_{10}$.
UF_S	1	A UF_S of 1 is applied because the study length (>35 d) is of an appropriate subchronic duration.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; DAP = diammonium phosphate; F = female(s); GLP = Good Laboratory Practice; LOAEL = lowest-observed-adverse-effect level; M = male(s); MAP = monoammonium phosphate; NOAEL = no-observed-adverse-effect level; OECD = Organisation for Economic Co-operation and Development; 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.

Because the determinant of the local toxicity (irritation) of DAP and MAP is expected to be the ammonium ion, the toxicity of these compounds is directly related to the relative molecular weight contribution from ammonium. Therefore, the screening subchronic p-RfD derived above for DAP is applicable to MAP following application of a molecular-weight adjustment and appropriate stoichiometric calculations.

Derivation of Screening Chronic Provisional Reference Dose

There are no adequate chronic-duration oral studies available for ammonium phosphate salts. The longest available study that could serve as the basis for toxicity assessment is the OECD 422 guideline study (combined repeated-dose toxicity study with reproductive/developmental screening test [Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)]). The systemic toxicity subgroup in that study was only treated for 35 days, which is not of adequate study duration for deriving a screening chronic p-RfD. In the reproductive component of the study, parental females were treated up to 53 days, which is of sufficient duration to derive a chronic value. In this case, however, stomach histopathology was only assessed in the systemic toxicity subgroup, which was treated for only 35 days. Because the critical effect was not assessed in the reproductive toxicity subgroup, it is unclear if the reproductive NOAEL of 1,500 mg/kg-day would be protective of stomach lesions caused by exposure to ammonium phosphate salts in a chronic setting. Therefore, derivation of a screening chronic p-RfD is not supported.

APPENDIX B. DATA TABLES

Table B-1. Comparison between Spirometry Findings in Workers at DAP (CASRN 7783-28-0) Fertilizer Plant and Controls[a]

Spirometry Parameter	Control (*n* = 68)	DAP Plant Workers (*n* = 30)
FVC (L)	3.43 ± 0.21[b]	2.51 ± 0.06* (−27%)[c]
FEV_1 (L)	2.84 ± 0.10	2.08 ± 0.08* (−27%)
PEFR/min (L/min)	383 ± 7.6	227.6 ± 18.2* (−41%)

[a]Bhat and Ramaswamy (1993).
[b]Mean ± SE (specified for controls in Table II of the publication).
[c]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by paired *t*-test ($p < 0.01$), as reported by the study authors.

DAP = diammonium phosphate; FEV_1 = forced expiratory volume of 1 second; FVC = forced vital capacity; PEFR = peak expiratory flow rate; SE = standard error.

Table B-2. Incidence of Minimal or Slight Submucosal Inflammation of the Stomach in Rats Exposed to DAP (CASRN 7783-28-0) by Gavage for 35 Days[a]

Dose (mg DAP/kg-d)	Male (%)	Female (%)	Combined (%)
0	0/5 (0)[b]	0/5 (0)	0/10 (0)
250	3/5 (60)	2/5 (40)	5/10* (50)
750	4/5* (80)	4/5* (80)	8/10* (80)
1,500	2/5 (40)	4/5* (80)	6/10* (60)

[a]Toxicity subgroup of Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002).
[b]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$) conducted for this review.

DAP = diammonium phosphate.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The benchmark dose (BMD) modeling of dichotomous data is conducted with the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS; Version 3.1.1 was used for this document). For these data, the Gamma, Logistic, Log-Logistic, Probit, Log-Probit, Hill, Multistage, and Weibull dichotomous models available within the software are fit using a benchmark response (BMR) of 10% extra risk. Alternative BMRs may also be used where appropriate, as outlined in the U.S. EPA's *Benchmark Dose Technical Guidance (*U.S. EPA, 2012*).* In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate benchmark dose lower confidence limit (BMDL) estimates from different models (high model dependence). Adequacy of model fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals (absolute value <2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD), if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

Dropping the High Dose

In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study's lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group may be reasonable for certain datasets.

Submucosal Inflammation of the Stomach in Rats Exposed to DAP by Gavage for 35 Days [Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)]

The procedure outlined above for dichotomous data was applied to the data for submucosal inflammation of the stomach in Sprague Dawley rats (both sexes combined) exposed to DAP via gavage for 35 days (see Table B-2). Table C-1 summarizes the BMD modeling results. With all dose groups included, the Log-Logistic, Log-Probit, and Hill models provided adequate fit ($p > 0.1$); however, the BMDs for these models varied widely (3 orders of magnitude); and the BMDLs for both the Log-Probit and Hill models were calculated as 0, while the Log-Logistic model yielded a BMDL estimate that was more than 12-fold lower than the lowest experimental dose. Because of these limitations when modeling the full dataset, and since the incidence at the high dose was lower than at the mid dose (750 mg DAP/kg-day), BMD modeling was then performed with the high-dose group removed from analysis, as consistent with *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). Without the highest dose group, additional model fit was obtained, with the Gamma, Log-Logistic, Multistage (2-degree and 1-degree), and Weibull models providing adequate fits to the data. Three separate, adequately fitting models (Gamma, Multistage [2-degree and 1-degree], and Weibull) also estimated the same BMD_{10} and $BMDL_{10}$ values of 44.3 and 27.7 mg/kg-day, respectively, with the Multistage

and Weibull models having the lowest AICs. Based on these more acceptable fits to the data after removing the high dose, a $BMDL_{10}$ of 27.7 mg/kg-day was identified for increased incidence of stomach submucosal inflammation (minimal/slight) in rats.

Table C-1. BMD Modeling Results for Submucosal Inflammation of the Stomach in Sprague Dawley Rats (Males and Females Combined) Administered DAP (CASRN 7783-28-0) via Gavage for 35 Days[a]

Model	*df*	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest (below) BMD	Scaled Residual at Dose Nearest (above) BMD[c]	AIC	BMD_{10} (mg DAP/kg-d)	$BMDL_{10}$ (mg DAP/kg-d)
Full dataset								
Gamma[d]	2	9.03	0.01	−0.0004	1.63	48.97	83.35	56.95
Log-Logistic[e]	3	3.80	0.28	−0.0004	0.56	42.69	39.48	19.94
Multistage (3-degree)[f]	2	9.03	0.01	−0.0004	1.63	48.97	83.35	56.95
Multistage (2-degree)[f]	3	9.03	0.03	−0.0004	1.63	46.97	83.35	56.95
Multistage (1-degree)[f]	2	9.03	0.01	−0.0004	1.63	48.97	83.35	56.95
Weibull[d]	2	9.03	0.01	−0.007	1.63	48.97	83.36	56.95
Dichotomous Hill	1	0.95	0.33	−0.0004	-4.08×10^{-5}	44.30	188.19	0.00
Logistic	2	9.33	0.01	−1.91	1.03	53.27	238.16	154.31
Log-Probit[e]	2	1.62	0.44	−0.0004	−0.39	43.04	0.17	0.00
Probit	2	9.36	0.01	−1.89	1.06	53.27	238.33	161.44
Highest dose dropped								
Gamma[d]	1	0.18	0.67	−0.0004	0.33	28.05	44.30	27.70
Log-Logistic[e]	1	1.52×10^{-7}	0.9997	−0.0004	1.72×10^{-7}	27.87	43.82	10.90
Multistage (1-degree)[f]*	**2**	**0.18**	**0.91**	**−0.0004**	**0.33**	**26.05**	**44.30**	**27.70**
Multistage (2-degree)[f]*	**2**	**0.18**	**0.91**	**−0.0004**	**0.33**	**26.05**	**44.30**	**27.70**
Weibull[d]*	**2**	**0.18**	**0.91**	**−0.0004**	**0.33**	**26.05**	**44.30**	**27.70**
Dichotomous Hill	−1	1.53×10^{-7}	65,535	−0.0004	-3.70×10^{-6}	31.87	47.58	0

Table C-1. BMD Modeling Results for Submucosal Inflammation of the Stomach in Sprague Dawley Rats (Males and Females Combined) Administered DAP (CASRN 7783-28-0) via Gavage for 35 Days[a]

Model	*df*	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest (below) BMD	Scaled Residual at Dose Nearest (above) BMD[c]	AIC	BMD_{10} (mg DAP/kg-d)	$BMDL_{10}$ (mg DAP/kg-d)
Logistic	1	3.05	0.08	−1.20	1.20	31.98	130.38	79.11
LogProbit[e]	0	1.78×10^{-7}	NA	−0.0004	-2.97×10^{-5}	29.87	46.92	0
Probit	1	3.01	0.08	−1.08	1.26	31.79	127.12	81.44

[a]Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals nearest BMDs were closest to the controls; therefore, scaled residual at nearest dose above (250 mg DAP/kg-day) were presented.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
*Best fitting model(s) identified in bold.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; DAP = diammonium phosphate; *df* = degrees of freedom; NA = not applicable (computation failed).

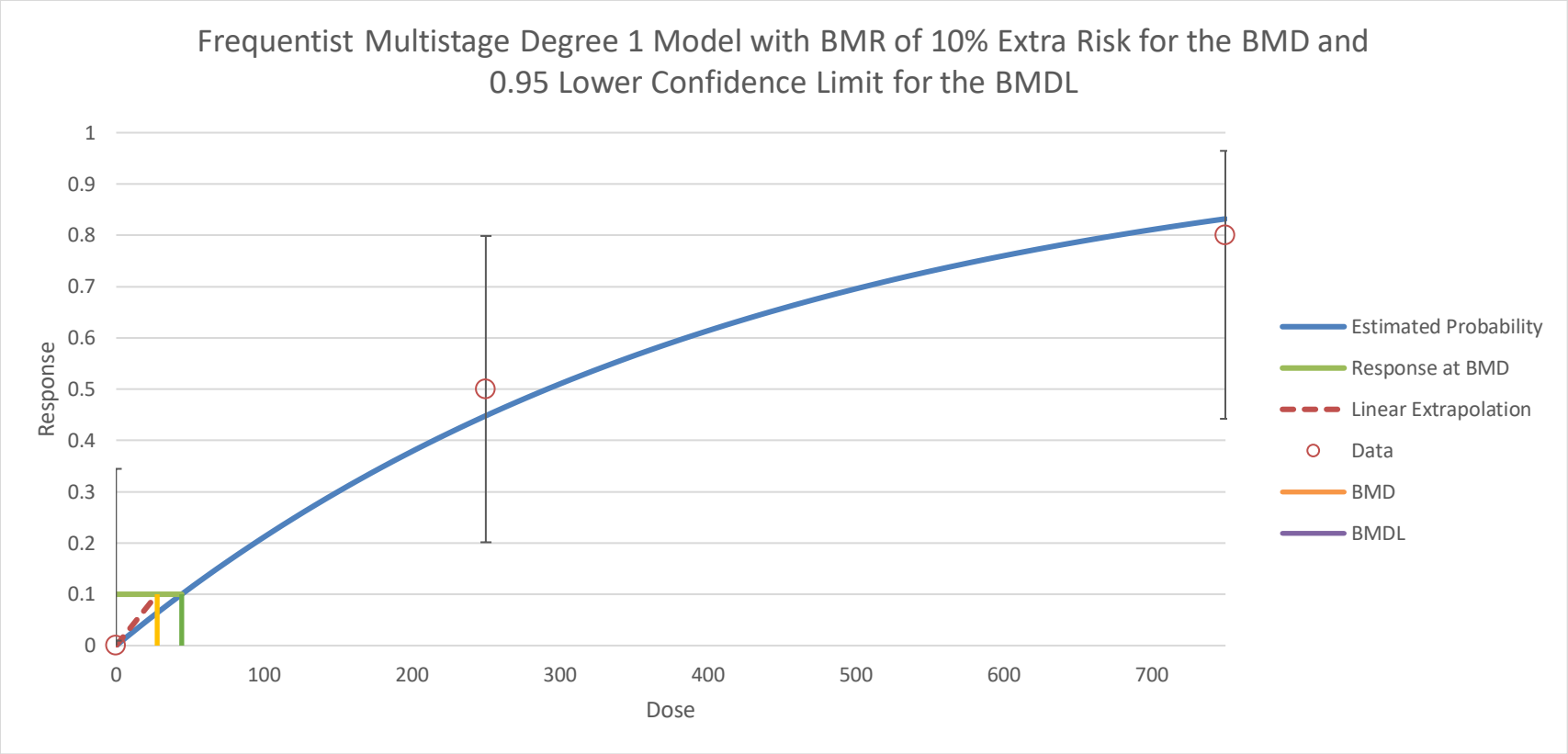

Figure C-1. Fit of Multistage (1-degree) Model to Data for Submucosal Inflammation of the Stomach in Sprague Dawley Rats (Males and Females Combined) Administered DAP (CASRN 7783-28-0) via Gavage for 35 Days [Huntingdon (2002) as cited in OECD (2007b) and ECHA (2002)]

APPENDIX D. REFERENCES

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