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Provisional Peer-Reviewed Toxicity Values for

Calcium Salts of Inorganic Phosphates (Multiple CASRNs)

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

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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 CALCIUM SALTS OF INORGANIC PHOSPHATES (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 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 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 is the basic unit for all phosphates. Condensed phosphates (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.

This document addresses the available data on the toxicity of calcium phosphate salts. Calcium phosphate salts are considered in this document separate from the other inorganic phosphates (sodium, potassium, ammonium, and aluminum phosphates) based on the expectation that the presence of calcium would influence the chemistry, toxicokinetics, and/or toxicity of the phosphate salt relative to the other classes of inorganic phosphates. Calcium phosphates are much less soluble than sodium or potassium phosphates (Gilmour, 2019). In addition, interactions between phosphate and calcium occur both in the intestine (where calcium phosphate formation reduces absorption of both ions) and in the kidney (where phosphate decreases urinary calcium excretion) [as reviewed by EFSA (2015)]. There is evidence that the ratio of calcium:phosphate (Ca:P) is an important determinant of phosphate toxicity; thus, administration of calcium phosphate might be expected to yield different toxicological effects than administration of sodium or potassium phosphate. The reader is referred to the PPRTV documents for sodium, potassium, ammonium, and aluminum phosphates for assessments of those inorganic phosphate salts.

All chemicals in this assessment are inorganic compounds consisting of PO_4^{3-} with calcium (CASRN 7440-70-2) at different ratios (1:1, 2:1, 1:2, etc.). Calcium, atomic number 20 is a member of the Group 2 alkaline earth metals. Calcium is the fifth most abundant element in the earth's crust (Vrana, 2011). Calcium is widely distributed in rocks, soils, and water (Vrana, 2011). In the environment and biological systems, calcium is found in complexes and salts (Vrana, 2011).

Calcium phosphates occur naturally and are found in living organisms. They are the main component of bone and teeth (Gilmour, 2019). Calcium phosphates occur as hydrated minerals, most commonly as deposits of apatite (Dorozhkin, 2009). Human exposure to calcium phosphates is expected to be common because they are used as food additives that are generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA, 2020, 2019). The calcium phosphate compounds (monocalcium phosphate [MCP], dicalcium phosphate [DCP], tricalcium phosphate [TCP], calcium pyrophosphate [CPP], and hydroxyapatite) are used in food. CPP is also used in toothpastes as an abrasive (NLM, 2020a, b, c, d, e). MCP is a leavening agent and acidulant in flour and baking soda; DCP and TCP are used as antacids; DCP, TCP, CPP, and hydroxyapatite are all used as dietary supplements for calcium and phosphorus (NLM,

2020a, b, c, d, e). The calcium phosphates are multiple-purpose food substances (182.1217), dietary supplements (182.5217, 182.5223), and nutrients (182.8217, 182.8223) classified by the FDA as GRAS when used in accordance with good manufacturing practice under Chapter 21 of the Code of Federal Regulations (FDA, 2020, 2019). MCP is also classified by the FDA as GRAS as a sequestrant (182.6215) (FDA, 2020).

The empirical formulas for several calcium phosphates are provided in Table 1A. Table 1B provides available information on the physicochemical properties of these compounds. All of the compounds in the table are listed in the U.S. EPA 2019 Toxic Substance and Chemical Act public inventory, with hydroxyapatite listed as Hydroxylapatite ($Ca_5(PO_4)_3OH$), CASRN 1306-06-5 (U.S. EPA, 2019), and are registered in Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (CASRNs 7758-23-8, 7757-93-9, 7758-87-4, 7790-76-3, 1306-06-5, and 12167-74-7) (ECHA, 2019a, b, c, d, e). The Inorganic Phosphates REACH Consortium substance information exchange forum considers CASRNs 1306-06-5 and 12167-74-7 to be the same substance, and many sources cite these two CASRNs for hydroxyapatite interchangeably (NLM, 2020e; Thornton, 2010). Di-, tri-, and tetra-hydrates of many of these chemicals with other CASRNs are also known.

Table 1A. Identity and Molecular Weight of Calcium Phosphates[a]

Compound	Synonym	CASRN	Molecular Formula	MW (g/mol)	Physical State
Phosphoric acid, calcium salt (2:1)	MCP, anhydrous	7758-23-8	$CaH_4P_2O_8$	234.05	Colorless pearly scales or powder[b]
Phosphoric acid, calcium salt (1:1)	DCP	7757-93-9	$CaHPO_4$	136.056	White crystalline powder[b]
Phosphoric acid, calcium salt (2:3)	TCP	7758-87-4	$Ca_3P_2O_8$	310.174	White crystalline powder[b, c]
Diphosphoric acid, calcium salt (1:2)	CPP	7790-76-3	$Ca_2P_2O_7$	254.097	White crystalline powder[d]
Calcium hydroxide phosphate	Hydroxyapatite	12167-74-7, 1306-06-5	$Ca_5HP_3O_{13}$	502.306	Solid, crystalline[b]

[a]U.S. EPA (2020a).
[b]NLM (2020a), NLM (2020b), NLM (2020c), NLM (2020e).
[c]ECHA (2010g).
[d]Schrödter et al. (2012).

CPP = calcium pyrophosphate; DCP = dicalcium phosphate; MCP = monocalcium phosphate; MW = molecular weight; TCP = tricalcium phosphate.

Table 1B. Physicochemical Properties of Calcium Phosphates

Compound	CASRN	Melting Point (°C)	Density (g/cm^3 at 25°C)	pH (unitless)	pKa (unitless)	Solubility in Water
MCP	7758-23-8	200	2.220 at 18°C[a]	NV	NV	Moderate solubility in water;[a] 93.9 g/L at pH 2.4[b]
DCP	7757-93-9	>450[c]	2.92[c]	6.5[c]	NV	Sparingly soluble in water;[a] 153 g/L at pH 6.5[d]
TCP	7758-87-4	1,670[c]	3.14[c]	NV	NV	Low solubility;[c] ≤20 mg/L at 20°C
CPP	7790-76-3	1,353[e]	2.866 at 20°C[f]	NV	NV	Practically insoluble in water;[e] <0.255 mg/L at pH 6.3−6.5[f]
Hydroxyapatite	12167-74-7, 1306-06-5	1,110 (decomposes)[a]	3.1−3.2[a]	NV	NV	Practically insoluble in water;[a] 6.57 mg/L at 20°C and pH 7.2−7.4,[g] 36.23 mg/L at 20°C based on calcium concentration, pH not reported[h]

[a]NLM (2020a), NLM (2020b), NLM (2020e).
[b]ECHA (2010a).
[c]OECD (2012), OECD (2011b).
[d]OECD (2011a), ECHA (2010b).
[e]Schrödter et al. (2012).
[f]ECHA (2015a), ECHA (2010c).
[g]ECHA (2010d).
[h]ECHA (2016).

CPP = calcium pyrophosphate; DCP = dicalcium phosphate; MCP = monocalcium phosphate; NV = not available; TCP = tricalcium phosphate.

Calcium phosphate compounds are more soluble in acidic conditions than buffered neutral or basic solutions. MCP and DCP have water solubility values of 93.9 and 153 g/L in unbuffered water, respectively. The addition of each chemical to the unbuffered water in the solubility test resulted in a final solution of pH 2.4 for MCP and 6.5 for DCP (ECHA, 2010e, f). MCP and DCP dissolve incongruently in water, with variations based on temperature and the amount of water (Gilmour, 2019). The water solubilities of several calcium phosphates are shown in Table 1B.

A summary of available toxicity values for calcium 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 Calcium Phosphate Salts (Multiple CASRNs)

Source (parameter)[a, b]	Phosphorus and Calcium Phosphates	Value (applicability)	Notes	Reference[c]
Noncancer				
IRIS	NA	NV	NA	U.S. EPA (2020b)
HEAST	NA	NV	NA	U.S. EPA (2011)
DWSHA	NA	NV	NA	U.S. EPA (2018)
ATSDR	NA	NV	NA	ATSDR (2020)
EFSA (AI)	P	AI by age: 7−11 mo: 160 mg/d 1−3 yr: 250 mg/d 4−10 yr: 440 mg/d 11−17 yr: 640 mg/d Adults and pregnant/lactating women: 550 mg/d	P from all sources.	EFSA (2015)
IOM (UL)	P	Children (1−8 yr): 3,000 mg/d Adolescents (9−18 yr): 4,000 mg/d Adults ≤70 yr: 4,000 mg/d Adults >70 yr: 3,000 mg/d Pregnant women: 3,500 mg/d Lactating women: 4,000 mg/d	The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. The UL represents total intake from food, water, and supplements.	IOM (1997)
IPCS/WHO (MTDI)	P	70 mg/kg BW	Maximum intake of P across all sources; based on nephrocalcinosis in rats.	WHO (1982)
CalEPA	NA	NV	NA	CalEPA (2020); CalEPA (2019)
OSHA	NA	NV	NA	OSHA (2020a); OSHA (2020b); OSHA (2020a)
NIOSH	NA	NV	NA	NIOSH (2018)
ACGIH	NA	NV	NA	ACGIH (2019)
USAPHC (air-MEG)	Dicalcium phosphate dihydrate (CASRN 7789-77-7)	1-h critical: 250 mg/m^3 1-h marginal: 50 mg/m^3 1-h negligible: 30 mg/m^3	Basis: TEELs	U.S. APHC (2013)
USAPHC (air-MEG)	Calcium phosphate; ratio not defined (CASRN 10103-46-5)	1-h critical: 350 mg/m^3 1-h marginal: 35 mg/m^3 1-h negligible: 20 mg/m^3	Basis: TEELs	U.S. APHC (2013)

Table 2. Summary of Available Toxicity Values for Calcium Phosphate Salts (Multiple CASRNs)

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

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; EFSA = European Food Safety Authority; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IOM = Institute of Medicine; 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: AI = adequate intake; MEG = military exposure guideline; MTDI = maximum tolerable daily intake; TEEL = temporary emergency exposure limit; UL = tolerable upper intake level.
[c]Reference date is the publication date for the database and not the date the source was accessed.

BW = body weight; NA = not applicable; NV = not available; P = phosphorus.

Literature searches were conducted in April 2019 and updated in March 2021 for studies relevant to the derivation of provisional toxicity values for the following calcium phosphate salts: MCP, DCP, TCP, and CPP. 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 Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), U.S. EPA TSCATS2/TSCATS8e, 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).

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

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 calcium phosphate salts, and include all potentially relevant repeated short-term, subchronic, and chronic studies as well as reproductive and developmental toxicity studies. 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, indicate a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Calcium Phosphate Salts (Multiple CASRNs)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, 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/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
Short term	**5 M/5 F, Sprague Dawley rat, DCP administered by gavage, daily for 28 d**	**0, 250, 500, 1,000 (as DCP)**	**No biologically relevant effects**	**1,000**	**NDr**	**NIER (2010) as cited in OECD (2011a)**	**PS, NPR, SS**
Short term, reproductive/ developmental	**10 M/10 F, Sprague Dawley rat; TCP administered by gavage, daily for 2 wk prior to mating, during mating, and up to a total of at least 28 d in M or throughout gestation, and until LD 4 in F**	**0, 250, 500, 1,000 (as TCP)**	**No biologically relevant effects**	**Parental: 1,000 Reproductive/ developmental: 1,000**	**NDr**	**NIER (2007) as cited in OECD (2012)**	**PS, NPR, SS**
Reproductive/ developmental	**13 M/13 F, Sprague Dawley rat; DCP administered by gavage, daily for 2 wk prior to mating, during mating, and until sacrifice in M (up to 42 d) or throughout gestation and until LD 4 in F**	**0, 250, 500, 1,000 (as DCP)**	**No biologically relevant effects**	**Parental: 1,000 Reproductive/ developmental: 1,000**	**NDr**	**NIER (2009) as cited in OECD (2011a)**	**PS, NPR, SS**
Developmental	25−29 mated F, albino Wistar-derived rat, MCP monohydrate administered by gavage, daily on GDs 6−15	0, 4.1, 19.1, 88.5, 410 (as MCP monohydrate)	No significant, treatment-related effects	Maternal and developmental: 410	NDr	FDRL (1974)	NPR
Developmental	23−26 mated F, albino CD-1 mouse MCP monohydrate administered by gavage, daily on GDs 6−15	0, 4.65, 21.6, 100, 465 (as MCP monohydrate)	No significant, treatment-related effects	Maternal and developmental: 465	NDr	FDRL (1974)	NPR

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

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Developmental	15−27 mated F, Dutch belted rabbit, MCP monohydrate administered by gavage, daily on GDs 6−18	0, 2.17, 10.10, 46.7, 217 (as MCP monohydrate)	No biologically relevant effects	Maternal and developmental: 217	NDr	FDRL (1974)	NPR
Developmental	5 pregnant F, Wistar rat, TCP (as food additive E341 obtained from Turkish bakery products company) administered by gavage, daily on GDs 0−20	0 (negative control), 0 (vehicle control), 175 (as TCP)	Increased transumbilical diameter, decreased left ulna and left femur lengths, decreased skull diameter	NDr	NDr	Güngörmüş et al. (2010) Study authors considered heavy metals in test material to be potential source of bone growth reduction	PR
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 and as HECs (in mg/m^3) for inhalation noncancer effects. In contrast to other repeated-exposure studies, values from animal gestational exposure studies are not adjusted for exposure duration in calculation of the ADD or HEC.
[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study; SS = available only as reported in secondary source.

ADD = average daily dose; DCP = dicalcium phosphate; F = female(s); GD = gestation day; HEC = human equivalent concentration; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCP = monocalcium phosphate; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; TCP = tricalcium phosphate.

Table 3B. Summary of Potentially Relevant Cancer Data for Calcium Phosphate Salts (Multiple CASRNs)				
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				

ND = no data.

2.1. HUMAN STUDIES

2.1.1. Oral Exposures

Human studies pertinent to the hazard assessment of oral exposure to calcium phosphate salts evaluated the effects of (1) calcium phosphate on bone endpoints in young girls (Bonjour et al., 2001a; Bonjour et al., 1997); (2) hydroxyapatite on bone in adults (Trautvetter et al., 2014); (3) DCP on intestinal obstruction (Cleghorn and Tudehope, 1981) and exercise performance (Galloway et al., 1996); and (4) TCP supplements on the incidence of gastrointestinal (GI) effects (O'Connell et al., 1989) and risk of colorectal cancer (Cats et al., 1993). These studies were not considered for quantitative assessment of noncancer effects because either the specific compound and/or dose of calcium phosphate used was not specified or no significant effects were observed.

Treatment of prepubertal girls with a calcium phosphate extract from milk (specific compound not specified) improved several measures of bone strength in a study conducted in Switzerland (Bonjour et al., 2001b; Bonjour et al., 1997). A group of healthy prepubertal girls between 6.6 and 9.4 years of age was recruited via the Geneva Public Health Youth Service between April and November of 1993. Only those girls whose baseline weight and height were between the 3rd and 97th percentiles for weight:height ratio were included. The exposure group was treated with a calcium phosphate extract from milk administered in food; the untreated group received placebo containing the same nutrient content without the calcium phosphate. Both groups were treated for 48 weeks. Dietary intake of calcium and phosphorus was evaluated via food frequency questionnaires administered before, during, and after treatment, and at follow-up. The mean contents of calcium and phosphorus in the test foods of the treated and placebo groups were 436 and 46 mg calcium and 236 and 54 mg phosphorus (respectively). Treated subjects were fed two calcium-enriched servings each day, providing an average calcium supplement of 870 mg calcium/day and 386 mg phosphorus/day. At baseline and 48 weeks later, anthropometric values (age, height, weight, and body mass index [BMI]) and bone variables (bone size, bone mineral content, and bone mineral density, assessed by dual-energy x-ray absorptiometry) at six skeletal sites (distal metaphysis of the radius, diaphysis of the radius, femoral neck, femoral trochanter, femoral diaphysis, and L2−L4 vertebrae) were measured (Bonjour et al., 1997). No significant effects on body weight or BMI were observed. Bone mineral content and bone area were increased (albeit not significantly) in the treated group relative to the placebo. At all skeletal sites, bone mass gains were greater in the treated group than in the placebo; these effects were significant ($p < 0.05$) for the radial diaphysis, femoral diaphysis, and femoral trochanter (and marginal for the radial metaphysis; $p < 0.08$). The effects on bone variables between the treated group and the placebo were more pronounced in girls with a lower than median spontaneous calcium intake (median 880 mg calcium/day). One year after discontinuation of treatment, differences in bone mass and size remained detectable. A total of 116 girls (62 treated and 54 placebo) participated in a follow-up evaluation 3.5 years after the end of treatment (Bonjour et al., 2001b). At this time, weight and height were measured; pubertal status was evaluated by questionnaire; and bone mineral content and bone mineral density were assessed. The two groups did not differ with respect to body weight, height, or pubertal status, nor were there group differences in dietary calcium intake. Overall mean bone mineral density, mean bone mineral content, and mean bone area were significantly ($p < 0.05$) higher in the treated group than the placebo group after controlling for pubertal maturation.

Trautvetter et al. (2014) conducted a double-blind, randomized, placebo-controlled study examining whether hydroxyapatite, provided as a supplement of approximately 1,000 mg calcium/day and 465 mg phosphorus/day on top of baseline) exhibited effects on bone

and mineral metabolism in 60 healthy subjects (24 men and 36 women, mean age 42 years). Hydroxyapatite was administered in bread for 4 or 8 weeks; at the end of exposure, blood and urine (24-hour sample) were collected for analysis of bone formation and resorption markers and calcium, phosphorus, magnesium, and iron; feces (3-day sample) was collected for analysis of calcium, phosphorus, magnesium, and iron. Hydroxyapatite supplementation for 4 or 8 weeks resulted in significantly ($p \leq 0.05$) decreased serum calcium and significantly increased fecal excretion of calcium and phosphorus; urinary calcium was not significantly different from placebo, and there were no significant effects on magnesium in any of the biological media. Plasma ferritin levels were lower after 4 and 8 weeks but not statistically significantly different from placebo. Decreased plasma 1,25-$(OH)_2$D (a metabolite indicative of vitamin D status) after 4 and 8 weeks of supplementation and statistically significantly increased plasma alkaline phosphatase (ALP) after 4 weeks of supplementation were observed with hydroxyapatite treatment; other bone-related hormones and markers of bone metabolism (plasma osteocalcin, serum parathyroid hormone [PTH], serum and urinary c-terminal telopeptide of type 1 collagen, serum N-terminal propeptide of type 1 procollagen, and urine deoxypyridinoline) were not affected by hydroxyapatite exposure. The study authors concluded that hydroxyapatite did not significantly affect bone remodeling.

O'Connell et al. (1989) compared gastrointestinal symptoms in adult female volunteers given different calcium supplements (TCP, calcium carbonate, or calcium citrate) or placebo in a double-blind study. Participants were women from Texas and Washington state who were treated as outpatients at Army medical facilities. Patients with hypercalcemia, kidney disease or kidney stones, diabetes, lactose intolerance, and gastrointestinal conditions were excluded. A total of 41 women (mean age 51.6 years) were selected to participate. Each supplement or the placebo was administered to the subjects for 7 consecutive days, followed by a 3-day washout period before the next treatment. TCP was administered as tablets containing 600 mg calcium per tablet (one tablet on awakening and a second at bedtime) which resulted in daily intake of 1,200 mg calcium and 620 mg phosphorus. At the end of each week of treatment, the patients completed questionnaires rating their GI symptoms (difficulty swallowing, belching, bloating, passing gas, diarrhea, constipation, cramping, and unpleasant taste) on a scale from 1 (none) to 4 (considerable) and overall tolerance of the supplement. The only symptom reported by a significant proportion of subjects treated with TCP was difficulty swallowing (mean score 1.78; 43.9% of scores were >1, compared with a mean score of 1.15 and 9.8% of scores >1 for placebo; $p = 0.07$).

In a study aimed at assessing whether TCP could reduce colorectal cancer risk by precipitating bile acids and fatty acids in the colon, Cats et al. (1993) administered TCP (39 mmol calcium and 26 mmol phosphate in tablet form) to 14 healthy volunteers (10 males, 4 females, mean age 30 years) daily for 1 week. Subjects were not treated during 1-week control periods before and after the treatment period. Fecal matter was collected before treatment, at the end of treatment, and 1 week after the end of treatment for assessment of pH, bile acid, and fat concentrations. Fecal water was analyzed for intestinal ALP activity (a marker for epithelial cell lysis) and cytolytic activity. Duodenal bile was collected before and after treatment for bile analysis. The only treatment-related changes were altered proportions of cholic and chenodeoxycholic acids (increased and decreased, respectively) in duodenal bile; these changes were not statistically significant compared with the control periods.

Intestinal obstruction in a premature male infant (born at 26 weeks of pregnancy) was attributed to treatment with a calcium hydrogen phosphate preparation (tradename DCP 340) in

combination with fluid restriction and diuretic therapy (Cleghorn and Tudehope, 1981). The infant had received diuretic and fluid restriction for treatment of pulmonary vascular congestion beginning at 12 days of age. DCP 340 was apparently administered as a nutritional supplement at the same time as these treatments, although the duration was not specified. The DCP 340 supplement contained 580 mg calcium and 450 mg phosphorus in 2.5 g powder, and 1.3 g of the preparation suspended in milk was given to the infant over 6 feeds. Intestinal obstruction was diagnosed by x-ray at some time between 12 and 28 days of age and successfully treated (Cleghorn and Tudehope, 1981). However, the study authors considered that the cause of intestinal obstruction might be attributed to dehydration predisposing to intestinal obstruction from viscous meconium.

In a crossover trial aimed at evaluating whether phosphate intake (single dose) improved exercise performance by stimulating erythrocyte glycolysis, Galloway et al. (1996) did not detect any effects of DCP treatment on measures of erythrocyte glycolysis or cardiorespiratory variables in exercising subjects. Small groups (n = 6/group) of high-fitness and low-fitness subjects (mean age 22−23 years) received a drink containing either 22.2 g DCP (equivalent to 317 mg DCP/kg-day) or calcium carbonate (placebo) and were subsequently asked to exercise. The two trials were 1 week apart. During each trial, the subjects exercised for 20 minutes (submaximal effort), rested for 30 minutes, and then exercised to exhaustion. Blood samples were collected before, during, and after the exercise segments and analyzed for erythrocyte 2,3-diphosphoglycerate, blood adenosine 5′-triphosphate (ATP), plasma lactate, plasma phosphate, hemoglobin [Hb], and hematocrit [Hct]. Oxygen uptake, minute ventilation, respiratory exchange ratio, heart rate, and oxygen pulse were recorded every 20−60 seconds during the exercise segments. Although there were differences between the high- and low-fitness subjects, no effect of DCP treatment was observed.

Several studies (Green et al., 2003; Yang et al., 1994; Guillemant and Guillemant, 1993; Reginster et al., 1993; Guillemant and Guillemant, 1991; Shires and Kessler, 1990) using very similar randomized crossover designs evaluated the effects of orally administered TCP on calcium homeostasis. In these studies, single doses of TCP containing 1,000−1,500 mg calcium and ~500−770 mg phosphorus increased serum and urinary levels of calcium and phosphorus, and decreased serum parathyroid hormone levels. Studies examining plasma calcitonin (Reginster et al., 1993) or urinary levels of nephrogenous cyclic adenosine monophosphate (cAMP) (Guillemant and Guillemant, 1993, 1991; Shires and Kessler, 1990) reported no changes in groups exposed to TCP. Green et al. (2003) also assessed biochemical markers of bone resorption in a group of 21 healthy postmenopausal women. In this group, serum c-telopeptide levels were lower after consumption of TCP in water compared with consumption of apple juice (control condition); urinary free deoxypyridinoline levels decreased with time after TCP intake, but the levels did not differ from those noted after apple juice intake.

2.1.2. Inhalation Exposures

No relevant human studies of inorganic phosphate inhalation have been identified in the literature searches.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

Only oral toxicity studies that clearly reported the phosphate compound used and the dose of compound administered were considered for dose-response assessment. Studies were not included that (1) did not clearly identify the test material, (2) cotreated animals with another test

substance, (3) did not use a vehicle control group, (4) simulated calcium and/or phosphate depletion, or (5) used genetically modified animals or animals in a diseased or injured state. Administered doses were based on the compound administered (rather than calcium and phosphorus separately) because calcium phosphate salts are relatively insoluble, and administration of these compounds would be expected to meet the minimal nutritional requirements for both calcium and phosphorus [approximately 5−6.3-g calcium/kg diet and 3.7-g phosphorus/kg diet for rats according to NRC (1995)]. Although the Ca:P ratio (present at about equimolar amounts in humans) is thought to be a determinant of toxicity (EFSA, 2015), administration of calcium phosphates is expected to minimally affect this ratio (because phosphorus and calcium homeostasis are both linked and tightly controlled) (EFSA, 2015).

The database of animal studies that examined the effects of oral intake of calcium inorganic phosphates, and that were considered for the dose-response assessment, consists of (1) several unpublished guideline studies available only from secondary sources (OECD, 2012, 2011a), including a 28-day repeated-dose toxicity study of DCP [NIER (2010) as cited in OECD (2011a)], a reproduction and developmental screening test of DCP [NIER (2009) as cited in OECD (2011a)], and a combined repeated-dose with reproductive and developmental toxicity study of TCP [NIER (2007) as cited in OECD (2012)]; (2) developmental toxicity studies of MCP monohydrate in rats, mice, and rabbits from an unpublished study report containing minimal study details (FDRL, 1974); and (3) a developmental toxicity study of a TCP food additive in rats (Güngörmüş et al., 2010). None of the studies specified the levels of phosphate (or calcium) in the basal diet, which is not critical because doses were given by gavage and expressed as administered compound.

Short-Term Studies

A 28-day repeated-dose toxicity study of DCP [NIER (2010) as cited in OECD (2011a)] and a combined repeated-dose with reproductive and developmental toxicity screen of TCP [NIER (2007) as cited in OECD (2012)] are unpublished and available only from secondary sources (OECD, 2012, 2011a). Unless otherwise specified, data for these studies were not shown in the secondary sources.

NIER (2010) as cited in OECD (2011a)

In an unpublished, Good Laboratory Practice (GLP)-compliant OECD Guideline 407 study, Sprague Dawley rats (5/sex/group) were administered DCP (CASRN 7757-93-9; purity 100%) via gavage in water at 0, 250, 500, or 1,000 mg DCP/kg-day for 28 days. Additional groups of control and high-dose animals (5/sex) were maintained for 2 weeks without dosing to evaluate the reversibility of any observed effects. Animals were monitored for mortality twice per day and clinical signs of toxicity once per day. Functional observations, including visual, auditory, and pain responses, aerial righting reflex, and motor activity were conducted during Week 4. Food consumption was measured once weekly (encompassing 6- or 7-day feeding periods). Body weights were recorded once weekly and 1 day prior to sacrifice. At Weeks 4 and 6, hematology (Hb; Hct; mean corpuscular volume [MCV]; mean corpuscular hemoglobin concentration [MCHC]; platelet, red blood cell [RBC], white blood cell [WBC], and reticulocyte [Ret] counts; prothrombin time [PT]; and activated partial thromboplastin time [APTT]), clinical chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], ALP, blood urea nitrogen [BUN], creatinine, glucose, total cholesterol, albumin:globulin [A:G] ratio, total protein, albumin, triglycerides, total bilirubin, and phosphorus), and urinalysis (volume, specific gravity, pH, protein, glucose, ketone bodies, bilirubin, occult blood, color, turbidity, and sediment) endpoints were evaluated. At necropsy, organ weights (of the brain, thyroid, lung, spleen,

adrenals, epididymis, prostate and seminal vesicle with coagulation gland, ovaries, thymus, heart, liver, kidneys, testes, and uterus) were recorded. Approximately 30 tissues were examined microscopically in animals from the control and 1,000-mg/kg-day groups.

No mortality occurred [NIER (2010) as cited in OECD (2011a)]. Other than discoloration of the stool (attributed to the white color of the test substance) at 500 and 1,000 mg/kg-day during dosing, no clinical signs of toxicity were observed. With respect to functional observations, a significant decrease in motor activity (vertical counts) was observed in 500-mg/kg-day females during the last 10-minute time interval only. This effect was not seen in conjunction with clinical signs, did not occur in any of the other five 10-minute intervals, was not seen in males, and occurred without dose-response in females. There were no statistically significant effects on food consumption, body weights, or clinical chemistry or urinalysis endpoints. At the end of the dosing and/or recovery periods, statistically significant effects on hematological endpoints (increased APTT in 500-mg/kg-day males and various effects in 1,000-mg/kg-day recovery females) and organ weights (increased relative liver weight in 250-mg/kg-day males) were not dose or duration related. Incidence data for macroscopic and microscopic findings were not provided; however, the secondary source (OECD, 2011b) indicated that all observed lesions in the stomach, thyroid, heart, kidney, liver, lung, pituitary, spleen, eye, and prostate occurred spontaneously and incidentally. Based on results of this study as reported to OECD and in the absence of data tables to facilitate an independent evaluation of the study results, a no-observed-adverse-effect level (NOAEL) of 1,000 mg DCP/kg-day (highest tested dose) is identified.

NIER (2007) as cited in OECD (2012)

In an unpublished, GLP-compliant OECD Guideline 422 combined repeated-dose and reproductive/developmental (R/D) toxicity study, Sprague Dawley rats (10/sex/group) were administered TCP (CASRN 7758-87-4; purity ≥96.9%) via gavage in 1% methylcellulose solution at 0, 250, 500, or 1,000 mg/kg-day during premating (2 weeks), mating, and postmating up to a total of at least 28 days (males) or throughout gestation, and until Lactation Day (LD) 4 (females). Additional recovery groups of control and 1,000-mg/kg-day animals (6/sex) were maintained for 21 days (males) or 22 days (females) after cessation of treatment. Females that showed no evidence of pregnancy were treated for up to 26 days after mating. Mortality and clinical signs of toxicity were monitored twice daily (before and after dosing). Body weights and detailed clinical observations were recorded weekly during premating, mating, and recovery. Food consumption was determined by comparing feeder weights on days body-weight measurements were recorded with empty feeder weights the following day. A functional observation battery (FOB), including cage observations; open field behavior; papillary constriction, approach, startle, tail pinch, and touch responses; Infra Mot (motor activity) test; and grip strength, was conducted for animals in the main study on the day prior to final dosing (males) or after separation of females from their pups on LD 4 (females). FOB endpoints were not evaluated in recovery animals (owing to the absence of effects at the end of the dosing period).

Clinical pathology and histopathological evaluations were performed for a subset of animals in the main study (5/sex/group, selected based on animal number and/or order of sacrifice) and in recovery animals. Just prior to sacrifice, animals were assessed for hematology (total and differential WBC, RBC, and platelet counts; Hb; Hct; MCV; mean corpuscular hemoglobin [MCH]; MCHC; PT; and APPT), clinical chemistry (AST, ALT, ALP, BUN, creatinine, glucose, total cholesterol, A:G ratio, total protein, albumin, creatine kinase,

triglycerides, total bilirubin, phospholipids, gamma glutamyl transferase, calcium, inorganic phosphorus, chloride, sodium, and potassium), and urinalysis (volume, specific gravity, pH, protein, ketone bodies, occult blood, glucose, bilirubin, nitrite, urobilinogen, color, clarity, and sediment in males only) endpoints. All animals were subjected to necropsy (males dosed on the day of sacrifice if not selected for urinalysis; females dosed until the day prior to sacrifice). Organ weights (of the brain, pituitary, adrenal gland, liver, spleen, kidneys, heart, thymus, lungs, salivary gland, thyroid, testes, epididymides, seminal vesicles, prostate, uterus, and/or ovary) were recorded (except in nonpregnant females). Over 40 tissues were examined microscopically in the control and 1,000-mg/kg-day groups; the kidneys were examined in all dose groups (including recovery groups).

No mortality was reported [NIER (2007) as cited in OECD (2012)]. Clinical signs of toxicity (scratched wounds and/or loss of fur) were reported; however, these effects were observed in no more than two animals per dose group during the treatment and/or recovery periods. Statistically significant effects on food consumption (decreased in 250-mg/kg-day males during premating and increased in 1,000-mg/kg-day females during recovery) were not dose or duration related. No significant treatment-related body-weight changes were observed. There were no adverse effects on FOB endpoints in males. In females, significantly decreased excretion of urine in an open field (all groups), increased ease of cage removal (250 mg/kg-day), and decreased grip strength of the hind limbs (500 and 1,000 mg/kg-day) were noted (magnitude of these changes not reported). According to OECD (2012), these effects were not considered by the submitter to be treatment related owing to the absence of a dose-response relationship, lack of effect on related endpoints (e.g., clinical signs of neurotoxicity), and no similar effect in males. There were no significant treatment-related effects on hematology, clinical chemistry, or urinalysis endpoints at the end of the dosing period. Significant effects on hematology endpoints observed in 1,000-mg/kg-day recovery groups included increased RBCs and decreased Ret in males and increased Hct in females. Recovery males also exhibited increased levels of serum phospholipids. The toxicological significance of these effects is uncertain because they were not observed at the end of dosing period.

The incidence of findings at necropsy was low; effects were observed in no more than one animal per dose group (including controls). With the exception of increased absolute (but not relative) brain weights in 250-mg/kg-day males, no significant organ-weight changes were observed at the end of the dosing period. At the end of the recovery period, significant organ-weight changes in the 1,000-mg/kg-day groups included increased absolute lung and relative liver weights in males, increased absolute salivary gland weight in females, decreased relative salivary gland weight in males, and decreased absolute and relative uterus weights in females. Various histopathological findings were reported during dosing period and recovery period; the majority of effects (affecting the liver, kidneys, spleen, heart, lung, pancreas, colon, rectum, seminal vesicle, and Harderian, thyroid, and pituitary glands) occurred in treated rats and controls without evidence of a dose-response relationship. There was some evidence for increased severity of renal mineralization (consistent with calcium deposits) in females (from minimal to minimal-to-slight) and for increased incidence and severity (from minimal to minimal-to-slight) of renal tubular degeneration/regeneration in males at the high dose of 1,000 mg/kg-day (see Table B-1). However, no statistically significant changes were observed. The submitter noted the absence of corresponding urinalysis, hematology, or clinical chemistry effects indicative of kidney damage (OECD, 2012). Based on results of this study as reported to OECD and in the absence of data tables to facilitate an independent evaluation of the study

results, a NOAEL of 1,000 mg TCP/kg-day (highest tested dose) is identified for parental animals. Results of the R/D toxicity screen are reported below.

Reproductive/Developmental Studies

Only one published study of reproductive or developmental effects in laboratory animals exposed orally to calcium inorganic phosphates was identified in the literature searches, that of Güngörmüş et al. (2010). There were several limitations (discussed below) associated with this study. Other reproductive and developmental toxicity studies of calcium inorganic phosphates were limited to developmental toxicity studies of MCP monohydrate available (in an incomplete form) from an unpublished report (FDRL, 1974), and unpublished guideline reproductive and/or developmental toxicity studies of DCP and TCP available only from secondary sources [NIER (2009) as cited in OECD (2011a); NIER (2007) as cited in OECD (2012)].

NIER (2007) as cited in OECD (2012)

In the repeated-dose toxicity study with reproduction/developmental toxicity screening test of TCP described above, reproductive and developmental endpoints evaluated included precoital time; numbers of corpora lutea and implantations; indices of mating, fertility, and pregnancy; gestation length; numbers of live and dead pups; litter size; and pup mortality, sex ratio, body weights, and external examinations. Based on the absence of significant, treatment-related effects on these endpoints (as reported to OECD and in the absence of data tables to facilitate an independent evaluation of the study results), a NOAEL of 1,000 mg TCP/kg-day (highest tested dose) is identified for reproductive and developmental toxicity.

NIER (2009) as cited in OECD (2011a)

In an unpublished, GLP-compliant OECD Guideline 421 study, Sprague Dawley rats (13/sex/group) were administered DCP (CASRN 7757-93-9; purity ≥98%) via gavage in water at 0, 250, 500, or 1,000 mg/kg-day during 2 weeks premating, mating, and until sacrifice (males; treated for up to 42 days) or throughout gestation and until LD 4 (females). Females that showed no evidence of pregnancy were treated for up to 26 days after mating. The animals were monitored regularly for mortality and clinical signs of toxicity. In males, food consumption and body weights were measured weekly during the dosing period (except food consumption during mating) and on the day prior to sacrifice. In females, food consumption was measured weekly (except during mating), on LDs 0 and 4, and on the day prior to sacrifice. Body weights were recorded at the same time points and additionally on GDs 0, 7, 14, and 20. All parental animals were subjected to necropsy, and testes, epididymides, ovaries, and uterus weights were recorded. Histopathological examinations of the testes, epididymides, and ovaries were performed for animals in the control and 1,000-mg/kg-day groups. Reproductive and developmental endpoints evaluated included numbers of implantation sites, mating and fertility indices, litter size, pup viability to Postnatal Day (PND) 4, and clinical signs, body weights, sex ratio, and external examinations of pups.

No mortality occurred [NIER (2009) as cited in OECD (2011a)]. Other than soft stool (in two 500-mg/kg-day males and one 1,000-mg/kg-day female), parental animals showed no clinical signs of toxicity. No significant, treatment-related effects on food consumption, body weights, or absolute or relative organ weights were observed. No macroscopic findings were reported; histological findings were confined to one control male, which showed bilateral evidence of seminiferous tubule atrophy (testes) and duct cell debris (epididymides). Indices of reproductive function were not significantly affected by treatment. Although pup mortality

occurred, the deaths did not seem to be treatment related. In the 0, 250, 500, and 1,000-mg/kg-day groups, mortality was 3.6, 1.3, 0.53, and 3.3%, respectively. Based on data provided in OECD (2011a), body weights of pups on PNDs 0 (males and females) and 4 (females) were not significantly affected by treatment. Conversely, pup weight was biologically significantly (≥5%) reduced in males on PND 4. However, given that this effect was marginal (only 5.7%) and only observed in males on PND 4, the toxicological relevance of this effect is unclear. In surviving pups of all dose groups, the incidence of external findings was zero (one 500-mg/kg-day pup that died was dwarf). Based on results of this study as reported to OECD and in the absence of data tables to facilitate an independent evaluation of the study results, a parental, reproductive, and developmental NOAEL of 1,000 mg DCP/kg-day (highest tested dose) is identified.

FDRL (1974)

Developmental toxicity studies of MCP monohydrate in rats, mice, and rabbits were obtained from an unpublished report containing appendices with minimal study details and some data tables (no measure of variation was provided, and no statistical analyses were performed). These studies did not specify the purity of the test substance and did not evaluate numbers of corpora lutea (except in rabbits) or uterine weights. Statistical analyses performed for this review were based on a significance level of $p < 0.05$.

Albino Wistar-derived rats (25−29 mated females/group) were administered MCP monohydrate (CASRN 10031-30-8) via gavage in water at 0, 4.1, 19.1, 88.5, or 410 mg/kg-day on Gestation Days (GDs) 6−15 and sacrificed on GD 20. Aspirin administered via gavage at 250 mg/kg-day served as a positive control for developmental toxicity. Maternal endpoints evaluated included mortality (in pregnant dams) and clinical signs of toxicity (monitored daily), food consumption (time points not specified), and body weights (measured on GDs 0, 6, 11, 15, and 20). At sacrifice, detailed examinations of the urogenital tract were performed. Numbers of implantations, resorptions, and live and dead fetuses were recorded. Fetuses were weighed, sexed, and evaluated for external abnormalities. Approximately one-third of the fetuses from each litter were subjected to visceral examinations (using the Wilson technique); remaining fetuses were evaluated for skeletal defects (using potassium hydroxide and alizarin red S).

The pregnancy rates in rats treated at 0, 4.1, 19.1, 88.5, and 410 mg/kg-day were 84, 79, 72, 76, and 88%, respectively (FDRL, 1974). No mortality was reported in pregnant dams. No information pertaining to clinical signs of toxicity or food consumption was provided. Maternal body weights were not adversely affected by treatment (i.e., the weights of treated dams were ≥90% of controls throughout the gestational period). The results of detailed examinations of the urogenital tracts of dams were not reported. All pregnant dams treated with MCP monohydrate produced a live litter. Based on statistical analyses performed for this review, there were no significant, treatment-effects on mean numbers of implantations or live fetuses. Based on data shown, fetal body weights and the sex ratio of fetuses were likewise unaffected by treatment. The incidence, if any, of external abnormalities was not reported. A soft tissue abnormality (hydrocephalus) was reported in one MCP monohydrate-treated rat (at 4.1 mg/kg-day). The number of fetuses per group evaluated for soft tissue abnormalities was not explicitly specified. Skeletal abnormalities (including ossification changes of the sternebrae, vertebrae, ribs, and skull) were prevalent in all dose groups, including controls. Based on statistical analyses performed for this review, the incidences of these effects were not significantly increased in MCP monohydrate-treated rats relative to controls (based on litter incidence). Treatment-related effects in rats administered the positive control substance (aspirin) included total litter loss (in

2/21 dams, owing to the resorption of all implantation sites), significant decreases in numbers of live fetuses (27% lower than controls) and fetal body weights (33% lower than controls), soft tissue anomalies (four fetuses with encephalomyelocele, meningoencephalocele, or gastroschisis), and significantly increased litter incidences of skeletal abnormalities (bipartite or missing sternebrae, fused/split ribs, incomplete ossification of vertebrae, and missing hyoid). In the absence of significant, treatment-related effects in MCP monohydrate-treated rats, 410 mg MCP/kg-day (highest tested dose) is identified as the NOAEL for maternal and developmental toxicity in rats.

Albino CD-1 mice (23−26 mated females/group) were administered MCP monohydrate (CASRN 10031-30-8) via gavage in water at 0, 4.65, 21.6, 100, or 465 mg/kg-day on GDs 6−15 and sacrificed on GD 17. Aspirin administered via gavage at 150 mg/kg-day was used as a positive control. The same maternal and developmental endpoints evaluated in the rat study were also evaluated in mice, except that maternal body weights were recorded in mice on GDs 0, 6, 11, 15, and 17.

The pregnancy rates in mice treated at 0, 4.65, 21.6, 100, and 465 mg/kg-day were 88, 96, 73, 96, and 92%, respectively (FDRL, 1974). In pregnant MCP monohydrate-treated dams, no mortality was reported. No information pertaining to clinical signs of toxicity or food consumption was provided. Maternal body weights were not adversely affected by treatment (i.e., the weights of treated dams were ≥90% of controls throughout the gestational period). The results of detailed examinations of the urogenital tracts of dams were not reported. One of 23 pregnant dams treated at 465 mg/kg-day failed to produce a live litter owing to the resorption of all implantation sites. Based on statistical analyses performed for this review, there were no significant treatment effects on mean numbers of implantations or live fetuses. Based on data shown, fetal body weights and the sex ratio of fetuses were likewise unaffected by treatment. The incidence, if any, of external abnormalities was not reported. No soft tissue anomalies were reported in MCP monohydrate-treated mice (number of fetuses evaluated per group was not explicitly specified). Skeletal abnormalities (including ossification changes of the sternebrae, vertebrae, and ribs) were prevalent in all dose groups, including controls. Based on statistical analyses performed for this review, the incidences of these effects were not significantly increased in MCP monohydrate-treated mice relative to controls (based on litter incidence). Treatment-related effects in mice administered the positive control substance (aspirin) included mortality (1/20 pregnant dams at GD 15) and soft tissue anomalies (cleft palate and gastroschisis in a single fetus). In the absence of significant, treatment-related effects in MCP monohydrate-treated mice, 465 mg/kg-day (highest tested dose) is identified as the NOAEL for maternal and developmental toxicity in mice.

Dutch belted rabbits (15−27 mated females/group) were administered MCP monohydrate (CASRN 10031-30-8) via gavage in water at 0, 2.17, 10.10, 46.7, or 217 mg/kg-day on GDs 6−18; kits of pregnant does were delivered by cesarean section on GD 29. 6-Aminonicotinamide (6-AN), administered via gavage at 2.5 mg/kg-day on GD 9, was used as a positive control. The maternal and developmental endpoints evaluated in the rat and mouse studies were also evaluated in rabbits, except that maternal body weights were recorded in rabbits on GDs 0, 6, 12, 18, and 29. In addition, the rabbit study evaluated numbers of corpora lutea and neonatal survival (for 24 hours); all fetuses were evaluated for visceral and skeletal abnormalities.

The pregnancy rates in rabbits treated at 0, 2.17, 10.10, 46.7, and 217 mg/kg-day were 57, 57, 63, 67, and 37%, respectively (FDRL, 1974). At the same doses (respectively), the incidence of mortality in pregnant does prior to GD 29 was 17, 8, 24, 0, and 0%. No information pertaining to clinical signs of toxicity or food consumption was provided. Maternal body weights were not adversely affected by treatment with MCP monohydrate. Although the body weights of does treated at 46.7 mg/kg-day were as much as 20% lower than controls during gestation, the weights of the rabbits in this dose group were only 83% of controls at study initiation (GD 0). The body weights of does in other MCP monohydrate treatment groups were ≥90% of controls for the duration of the study. The incidences of total litter loss owing to resorption of all implantation sites were 0, 9, 0, 10, and 20% while partial resorption rates were 40, 18, 15, 40, and 20% at 0, 2.17, 10.10, 46.7, and 217 mg/kg-day, respectively. Owing to the low pregnancy rate, combined with mortality and pregnancy loss, the number of pregnant rabbits that carried to term (GD 29) ranged from 10 to 13 per MCP monohydrate-treatment group. Based on statistical analyses performed for this review, the numbers of corpora lutea were significantly decreased at 217 mg/kg-day (44% lower than controls; see Table B-2). However, this effect was not accompanied by significant and/or treatment-related changes in mean numbers of implantations, resorptions, or live fetuses. Based on data shown, fetal body weights and the sex ratio of fetuses were unaffected by treatment (a reduction in fetal body weights of 9% at 46.7 mg/kg-day was likely secondary to reduced maternal body weights at the same dose level). No data for neonatal survival were provided. The incidence, if any, of external abnormalities was not reported. No soft tissue anomalies were reported in MCP monohydrate-treated rabbits (number of fetuses evaluated per group was not explicitly specified). Skeletal abnormalities (i.e., effects on ossification) were seen in no more than one litter per control or treatment group and without evidence of a dose-related response. No treatment-related effects were observed in rabbits administered the positive control substance (6-AN). Decreased numbers of corpora lutea at 217 mg MCP monohydrate/kg-day, in the absence of effects on the numbers of implantations and live fetuses, was not considered to be biologically relevant for this review. Therefore, 217 mg MCP/kg-day is identified as the NOAEL for maternal and developmental toxicity in rabbits.

Güngörmüş et al. (2010)

Wistar rats (five pregnant females/group) were administered TCP (CASRN 7758-87-4) via gavage in corn oil at 0 (untreated control), 0 (vehicle control), or 175 mg/kg-day on GDs 0−20. Although the purity of the test substance (reportedly obtained from a bakery products company) was not specified, it was indicated that microbiological contaminants (including live bacteria, *Coliform*, *Escherichia coli*, *Salmonella*, and mold) were present at <1,000/g and other contaminants (arsenic, lead, cadmium, mercury, total heavy metals, and copper) were present at <30 ppm. Maternal animals were monitored for mortality and clinical signs of toxicity. At sacrifice on GD 20, the numbers of live and dead fetuses were recorded; fetal body weights and crown-rump length were measured. The diameter, length, and thickness of the placenta were evaluated; the placental index was calculated as placental weight divided by fetal body weight. The transumbilical diameter was recorded. The morphology of the placenta and the umbilical cord was examined grossly. All fetuses were subjected to skeletal examinations (using alcian blue to stain cartilage and alizarin red S to stain bone). Fetuses were also subjected to morphological examinations using stereomicroscopy, including length and diameter of the skull, length of the fore- and hindlimbs, and numbers of vertebrae and ribs.

Unless otherwise specified, the effects in TCP-treated animals were compared with those of the vehicle control group (Güngörmüş et al., 2010). No mortality or clinical signs of toxicity

were observed in maternal animals. There were no significant, treatment-related effects on the numbers of pups per litter, fetal body weights, or crown-rump length. No gross fetal abnormalities were reported. The diameter, length, and thickness of the placenta were similar among treated and control groups. Placenta weight was significantly decreased in rats treated at 175 mg/kg-day compared with untreated controls but not vehicle controls (see Table B-3). There were no significant effects on the placental index based on comparison to either control group. Transumbilical diameter was significantly increased at 175 mg/kg-day (8% higher than vehicle controls). Morphology of the placenta was normal in the treated group and controls (i.e., whole, discoidal-shaped, and central rather than ovoid, two-lobbed, or marginal). Changes in gross morphology of the umbilical cord, if any, were not reported. Staining of fetuses showed no evidence of skeletal anomalies; ossification (of sternebrae, limbs, and sacral and caudal bones) was complete and there were no discrepancies in bone number. Morphological analyses showed that treated rats had significantly decreased left ulna and left femur lengths (29% less than vehicle controls); the diameter of the skull (*y*-axis) was significantly impacted based on comparison to the untreated control group only. Right ulna and femur lengths were also decreased (by 29 and 21%, respectively); however, these changes were not statistically significant. The toxicological significance of increased transumbilical diameter and unilateral reductions in bone size (significantly decreased left ulna and left femur lengths without significant effects on the right ulna/femur or on adjacent bones such as the humerus, radius, tibia, or fibula) is uncertain. Owing to these factors and study limitations, such as small group sizes, testing of only a single dose level, and use of test material that contained heavy metal contaminants and unknown purity, no NOAEL or lowest-observed-adverse-effect level (LOAEL) for this study is identified.

2.2.2. Inhalation Exposures

No relevant animal studies of inorganic phosphate inhalation have been identified in the literature searches.

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

2.3.1. Genotoxicity

Table 4A provides an overview of genotoxicity studies of calcium inorganic phosphates. Data pertaining to the genotoxicity of calcium phosphate salts (all negative) are derived primarily from unpublished studies and/or secondary sources. MCP, DCP, TCP, and CPP were not mutagenic to *Salmonella typhimurium* and/or *E. coli* with or without metabolic activation [NIER (2006) as cited in OECD (2011a); NIER (2009) as cited in OECD (2012); Litton Bionetics (1975); Litton Bionetics (1976); ECHA (2015b)]. Neither MCP nor TCP were mutagenic in *Saccharomyces cerevisiae* strain D4 (Litton Bionetics, 1976, 1975), and CPP did not induce mutations in mouse L5178Y/TK+/− lymphoma cells. Data also provide no evidence for clastogenicity. DCP did not induce chromosomal aberrations (CAs) in Chinese hamster lung (CHL) cells [NIER (2006) as cited in OECD (2011a)]. The incidence of micronuclei formation in CHL (V79) cells in vitro was not increased by treatment with CPP with or without metabolic activation (ECHA, 2015d). No in vivo genotoxicity data for calcium phosphate salts were identified.

Table 4A. Summary of Calcium Phosphate Salts (Multiple CASRNs) Genotoxicity						
Endpoint and Substance	**Test System**	**Doses/ Concentrations Tested[a]**	**Results without Activation[b]**	**Results with Activation[b]**	**Comments**	**References**
Genotoxicity studies in prokaryotic organisms						
Mutagenicity MCP	*Salmonella typhimurium* strains TA1535, TA1537, and TA1538	0.75%	–	–	Plate and suspension tests; activation from tissues of rat, mouse, or monkey	Litton Bionetics (1975)
Mutagenicity DCP	*S. typhimurium* strains TA1535, TA1537, TA98, and TA 100, *Escherichia coli* WP2 uvrA	1,250 µg/plate	–	–	OECD 471 and GLP study; preincubation method; positive and negative controls responded appropriately	NIER (2006) as cited in OECD (2011a)
Mutagenicity TCP	*S. typhimurium* strains TA1535, TA1537, and TA1538	0.00053%	–	–	Plate and suspension tests; activation from tissues of rat, mouse, or monkey	Litton Bionetics (1976)
Mutagenicity TCP	*S. typhimurium* strains TA 1535, TA1537, TA98, and TA100, *E. coli* WP2 uvrA	1,250 µg/plate	–	–	OECD 471 and GLP study; plate incorporation method; precipitate observed at 1,250 µg/plate without activation; positive and negative controls responded appropriately	NIER (2009) as cited in OECD (2012)
Mutagenicity CPP	*S. typhimurium* strains TA1535, TA1537, TA98, and TA100, *E. coli* WP2 uvrA	5,000 µg/plate	–	–	OECD 471 and GLP study; preincubation method; no evidence of cytotoxicity; positive and negative controls responded appropriately	ECHA (2015b)
Genotoxicity studies in nonmammalian cells—in vitro						
Mutagenicity MCP	*Saccharomyces cerevisiae* strain D4	5.0%	–	–	Suspension tests; activation from tissues of rat, mouse, or monkey	Litton Bionetics (1975)
Mutagenicity TCP	*S. cerevisiae* strain D4	5.0%	–	–	Suspension tests; activation from tissues of rat, mouse, or monkey	Litton Bionetics (1976)

Table 4A. Summary of Calcium Phosphate Salts (Multiple CASRNs) Genotoxicity

Endpoint and Substance	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies in mammalian cells—in vitro						
Mutagenicity CPP	Mouse lymphoma L5178Y cells	625 µg/mL	−	−	OECD 476 and GLP study; slight precipitation at all concentrations; no evidence of cytotoxicity; positive and negative controls responded appropriately	ECHA (2015c)
CAs DCP	CHL cells	500 µg/mL	−	−	OECD 473 and GLP study; positive and negative controls responded appropriately	NIER (2006) as cited in OECD (2011a)
CAs TCP	CHL cells	NR	NR	NR	OECD 473 and GLP study	NIER (2005) as cited in OECD (2012)
Micronucleus assay CPP	CHL fibroblasts (V79)	3.2 µg/mL	−	−	OECD 487 and GLP study; slight precipitation at 3.2 µg/mL; no evidence of cytotoxicity; positive and negative controls responded appropriately; deviations included duration of extended treatment not specified and no historical vehicle or positive control data	ECHA (2015d)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive; ± = weakly positive; − = negative.

CA = chromosomal aberration; CHL = Chinese hamster lung; CPP = calcium pyrophosphate; DCP = dicalcium phosphate; GLP = Good Laboratory Practice; MCP = monocalcium phosphate; NR = not reported; OECD = Organisation for Economic Co-operation and Development; TCP = tricalcium phosphate.

2.3.2. Initiation-Promotion

At least one study has examined the potentially protective effect of calcium supplementation on tumorigenesis. F344 rats were injected with 1,2-dimethylhydrazine and subsequently administered diets containing DCP dihydrate at about 2,700- (control) or 31,000-mg/kg diet (with or without the addition of 60% beef) for 100 days and evaluated for effects on colorectal carcinogenesis (Pierre et al., 2008). Based on data provided for the composition of the diets and reference food consumption (0.0141 kg/day) and body-weight (0.124 kg) data for female F344 rats, these doses were equivalent to about 240−310 and 3,800 mg DCP dihydrate/kg-day. Compared with the control (low calcium) diet, rats administered 31,000-mg DCP dihydrate/kg diet showed increased numbers of precancerous lesions (aberrant crypt foci [ACF] and mucin-depleted foci [MDF]) in the colon. Fecal mass was significantly increased, and the cytotoxicity of fecal water (based on lysis of CMT 93 cells) was significantly decreased. Rats administered beef in the diet (at 60%) also showed significantly increased numbers of ACF and MDF, as well as increased cytotoxicity and lipid peroxidation (measured as thiobarbituric acid-reactive substances [TBARS]) in fecal water, and increased urinary 1,4-dihydroxynone mercapturic acid (DHN-MA; a marker of heme-induced promotion) excretion. In rats administered diets containing beef supplemented with 31,000-mg DCP dihydrate/kg diet, ACFs and MDFs (expressed as numbers of ACFs or MDFs/colon), TBARS, and cytotoxicity of fecal water were normalized (to control-like levels). However, the number of crypts per ACF or MDF remained significantly increased in this group than in controls. There was no effect on DHN-MA.

2.3.3. Acute Toxicity

Based on unpublished data from secondary sources, calcium phosphate salts exhibit low acute lethal potential. Unpublished acute oral lethality studies performed according to OECD Guideline 423 were reported in OECD (2011a) and OECD (2012). The median lethal dose (LD_{50}) values determined in rats were >2,000 mg/kg for DCP and TCP, and no mortality, clinical signs, or macroscopic findings were reported [NIER (2006) as cited in OECD (2012) and NIER (2008) as cited in OECD (2011a)]. In a review, Weiner et al. (2001) reported the following oral LD_{50} values for rats: >1,000 and 2,170 mg/kg for MCP; 7,100, >7,940, and ≤10,000 mg/kg for DCP; >5,000 mg/kg for TCP; and >10,000 mg/kg for CPP, citing unpublished studies by Stauffer, Solutia, and Albright and Wilson. An LD_{50} of 4,600 mg/kg for MCP was reported in mice (citing an unpublished study by IPCS).

In an acute oral lethality study of MCP in rats, a gavage dose of 5,000 mg/kg resulted in mortality incidences of 3/10 in males and 7/10 in females; LD_{50} values from these data were >5,000 and 3,986 mg/kg, respectively (Stauffer Chem Co, 1992). Clinical signs of toxicity (depression, diarrhea, piloerection, and ptosis) were observed, and necropsy commonly showed mottled and/or pale lungs, livers, and kidneys, and darkened spleens.

One unpublished acute inhalation toxicity study, performed according to OECD Guideline 403, was reported in ECHA (2011) as cited in OECD (2011a). The 4-hour median lethal concentration (LC_{50}) value for MCP determined in male and female rats was >2.6 mg/L air (highest achievable concentration); no mortality occurred. Transient clinical signs of toxicity (ruffled fur) and body-weight loss were noted; no findings were reported at gross necropsy.

Stauffer Chem Co (1992) reported results of rabbit dermal lethality studies of MCP solution in which LD_{50} value >2,000 was estimated. In the MCP study, no mortality, clinical

signs of toxicity, or macroscopic effects were noted; severe erythema and mild edema occurred at the application site (Stauffer Chem Co, 1992).

Additional data on acute dermal toxicity are available from a secondary source. Weiner et al. (2001) reported the following dermal LD_{50} values for rabbits: >300 mg/kg for MCP, >7,940 mg/kg for DCP, >2,000 mg/kg for TCP, and >7,940 mg/kg for CPP, citing unpublished studies by Stauffer, Solutia, and Albright and Wilson.

MCP was considered nonirritating when applied to the skin and severely irritating and corrosive to the eyes in tests conducted in rabbits (Stauffer Chem Co, 1992). Effects observed included corneal opacity, iridial inflammation, and conjunctivitis; effects on the eyes were irreversible. According to Weiner et al. (2001), divalent phosphate salts (DCP, TCP, and CPP were generally considered either nonirritating or slightly to mildly irritating when applied to the skin and eyes in tests conducted in rabbits.

2.3.4. Other Animal Studies

Other animal studies are summarized in Table 4B. Most of these studies focused on the effects of calcium supplementation on the gut (most often when the control diet contained low or possibly inadequate levels of calcium). Animals administered DCP or DCP dihydrate in the diet showed changes in excretion patterns, including (most frequently) increased fecal output (Paßlack et al., 2016; Sprong et al., 2002; Govers et al., 1994), increased excretion of calcium and phosphorus in the feces and/or urine (Paßlack et al., 2016; Sprong et al., 2002; Govers et al., 1994), and decreased fatty acids, bile acids, and cytotoxicity (as measured by erythrocyte lysis) in fecal water or ileal lavage (Sesink et al., 2001; Bovee-Oudenhoven et al., 1999; Govers et al., 1994; Lapré et al., 1993). A few studies showed that DCP or DCP dihydrate supplementation decreased cell damage (as measured by ALP release) and/or indices of colonic cell proliferation (Lupton et al., 1995; Govers et al., 1994; Lapré et al., 1993). In one study (Bovee-Oudenhoven et al., 1999), supplementation with DCP dihydrate was shown to increase the numbers of endogenous bacteria in the gut, thereby generating an environment that was less susceptible to exogenous bacterial infection.

Table 4B. Other Studies

Strain/Species/ Sex/Number	Mode/Duration	Dose Administered	Results	Reference (notes)
F344 rat; 5 F/group	Diet, 7 d	20 (control), 33, 55, 90, 150, or 250-mmol DCP/kg diet (equivalent to about 230, 450, 800, 1,200, 2,200, or 3,700 mg DCP/kg-d based on reference body weight [0.124 kg] and food consumption [0.0141 kg/d] values for female F344 rats)	No treatment-related effects on food consumption or body weights were observed. At 150- and 250-mmol DCP/kg diet, heme was significantly decreased in fecal water; however, heme-induced lipid peroxidation (measured by TBARS level) was not significantly affected by treatment.	Allam et al. (2011) (Low calcium, beef-based diets containing 60% meat.)
European shorthair cat; 5/sex	Diet, 8 d (each diet, separated by 10 d adaptation periods)	0.6, 0.8, 1.5, 1.9, 2.2, or 2.4% Ca/kg diet as DCP	No treatment-related effects on food consumption (after exclusion of two 2.4% cats that refused food) or body weights were observed. Levels of vitamin D and vitamin D metabolites, PTH and FGF23, in the serum were not affected by treatment. Based on linear contrast analyses, effects observed with increasing calcium-phosphorus concentrations included decreased levels of serum calcitriol precursors, decreased urine pH (fasting and nonfasting), increased urine phosphorus, increased total fecal output, and increased fecal calcium and phosphorus; a number of these effects were not strictly dose related.	Paßlack et al. (2016) (0.6 and 0.8% diets were considered low calcium; 1.9 to 2.4% diets were high calcium; doses of DCP administered were not specified.)
Wistar rat, 8 M/group	Diet, 10 d (with *Salmonella enteritidis* infection via gavage on study Day 10)	20 (control) or 180-mmol DCP dihydrate/kg diet (equivalent to about 210 or 1,900 mg DCP dihydrate/kg-d based on body-weight and food-consumption data provided)	Treatment with DCP dihydrate did not affect body-weight gain. Noninfected rats treated at 180-mmol DCP dihydrate/kg diet (and evaluated 6 d following treatment) showed significantly decreased cytotoxicity (based on lysis of erythrocytes), bile acids, and fatty acids in ileal lavage and fecal water. Concentrations of unconjugated bile acids in ileal lavage acids were significantly decreased, and ileal contents/scrapings and feces contained increased numbers of endogenous lactobacilli. Relative to infected controls, rats treated at 180-mmol DCP dihydrate/kg diet and subsequently infected with *S. enteritidis* showed significantly decreased fecal *Salmonella* excretion 1, 3, and 6 d postinfection; decreased urinary NO_X excretion 4, 5, and 6 d postinfection (indicative of decreased bacterial translocation); decreased bile acids and fatty acids in ileal lavage; and decreased numbers of viable *Salmonella* in ileal lavage/scrapings 6 d postinfection.	Bovee-Oudenhoven et al. (1999) (Diets had a high fat content; the control diet also had low calcium to mimic a Western human diet.)

Table 4B. Other Studies

Strain/Species/ Sex/Number	Mode/Duration	Dose Administered	Results	Reference (notes)
Sprague Dawley rat, 10 M/group	Gavage, 14 d	0 or 214 mg DCP/kg-d	No significant, treatment-related effects on mortality, clinical signs of toxicity, or gross pathology were observed.	ECHA (1970)
Wistar rats, 7 M/group	Diet, 14 d (with $CaCO_3$ or dairy milk as alternative calcium sources)	30-mmol calcium/kg diet as DCP (control) or 150-mmol DCP/kg diet (equivalent to about 1,200 mg DCP/kg-d based on the body-weight and food-consumption data provided)	No treatment-related effects on food consumption or body weight were observed. Rats treated with DCP showed significantly increased fecal output (dry weight), increased fecal concentrations of calcium, phosphate, and total fatty acids, and significantly decreased levels of soluble bile acids, soluble fatty acids, and cytotoxicity in fecal water (based on lysis of erythrocytes). DCP-treated rats also showed a significant reduction in the release of ALP (a potential marker of epithelial cell damage) and decreased colonic epithelial cell proliferation (despite significantly increased serum gastrin, which is thought to stimulate colonic epithelial cell proliferation).	Govers et al. (1994) (Diets designed to mimic a Western high-risk diet.)
Wistar rat, 7 M/group	Diet, 14 d (in conjunction with palm oil, milk fat, or corn oil as sources of dietary fat)	25 (control) or 225-mmol DCP dihydrate/kg diet (equivalent to about 410 or 3,700 mg DCP dihydrate/kg-d based on food consumption data provided and a reference body weight of 0.217 kg for male Wistar rats)	No treatment-related effects on food consumption or body-weight gain were observed. Rats treated at 225-mmol DCP dihydrate/kg diet showed increased total fecal fatty acid excretion. However, concentrations of soluble fatty acids and bile acids (as measured in fecal water) were significantly decreased, and consequently, the cytotoxicity of fecal water samples was significantly decreased (based on lysis of erythrocytes). DCP dihydrate-treated rats also showed decreased intestinal epitheliolysis (as evidenced by decreased ALP activity, a possible marker for intestinal cell damage, in fecal water samples).	Lapré et al. (1993) (Control diets were low in calcium to mimic a Western human diet.)
Wistar rats, 8 M/group	Diet, 14 d	20 (control) or 180-mmol DCP dihydrate/kg diet (equivalent to about 220 or 2,100 mg DCP dihydrate/kg-d based on body-weight and food-consumption data provided)	No treatment-related effects on food consumption or body-weight gain were observed. Rats treated at 180-mmol DCP dihydrate/kg diet showed significantly increased fecal output (dry weight); levels of calcium and phosphate were increased in fecal water. There were no significant, treatment-related effects on fecal cations, cytotoxicity of the fecal water (based on lysis of erythrocytes), or colonic epithelial cell proliferation.	Sesink et al. (2001) ("Low calcium" control diet; additional groups were administered 1.3 mmol heme with or without DCP dihydrate.)

Table 4B. Other Studies

Strain/Species/ Sex/Number	Mode/Duration	Dose Administered	Results	Reference (notes)
Wistar rat, 6−8 M/group	Diet, 17 d (in conjunction with corn oil or milk fat as a source of dietary fat and *Listeria monocytogenes* infection on study Day 14)	20 (control) or 160-mmol DCP dihydrate/kg diet (equivalent to about 190 or 1,700 mg DCP dihydrate/kg-d based on body-weight and food-consumption data provided)	Treatment with DCP dihydrate did not affect food consumption or body-weight gain. Rats treated at 180-mmol DCP dihydrate/kg diet showed significant increases in total fecal output, calcium, phosphate, and free fatty acids in the feces, and calcium in fecal water; concentrations of bile salts and free fatty acids (corn oil diet only) in fecal water were significantly decreased. Relative to infected corn oil controls, rats treated at 180-mmol DCP dihydrate/kg diet (corn oil diet) and subsequently infected with *L. monocytogenes* showed significantly increased excretion of viable *Listeria* and increased urinary NO_X excretion (indicative of decreased bacterial translocation) 3 d postinfection. There was also significantly increased ex vivo growth of *Listeria* in fecal extracts. There were no significant effects on any of these endpoints in rats treated with DCP dihydrate/milk fat diet (compared with infected, milk fat controls).	Sprong et al. (2002)
Sprague Dawley rat, 12 M/group	Diet, 21 d (with calcium casein, calcium lactate, or $CaCO_3$:$CaPO_4$ as alternative calcium sources)	Not reported; calcium phosphate (identified in the study as $CaPO_4$) at 0.5% calcium by weight	No treatment-related effects on food consumption, body weight/body-weight gain, fecal output, fecal lipid content, surface area of the cecum, or large intestine length were observed. Compared to other sources of calcium, rats treated with calcium phosphate showed significantly decreased cecum pH in vivo (with no significant effects on pH in the proximal or distal colon). Compared with other forms of calcium supplementation (i.e., calcium lactate), calcium phosphate treatment resulted in significantly decreased cell proliferation in the proximal colon (e.g., lower numbers of cells/crypt column and a lower labeling index); there were no significant effects on the distal colon or cecum. Calcium phosphate (and calcium caseinate) altered concentrations of bile acids in the feces; total bile acids and the levels of some secondary bile acids (i.e., lithocholate and β-muricholate) were significantly decreased compared with other groups.	Lupton et al. (1995) (Diets contained a high fat content; doses of calcium phosphate administered were not specified.)

ALP = alkaline phosphatase; Ca = calcium; $CaCO_3$ = calcium carbonate; $CaPO_4$ = calcium phosphate; DCP = dicalcium phosphate; F = female(s); FGF23 = fibroblast growth factor 23; M = male(s); NO_X = nitric oxide; PTH = parathyroid hormone; TBARS = thiobarbituric acid-reactive substances.

2.3.5. Metabolism/Toxicokinetic Studies

Absorption of calcium phosphate salts is expected to be low via the inhalation and dermal routes of exposure owing to their high molecular weight and low solubility (ECHA, 2020a, b, c, d). Experiments in animals and humans have shown that calcium salts also exhibit low to moderate absorption via the oral route of exposure (ECHA, 2020a, b, c, d). In aged female rats administered 4- or 8-mg calcium/g diet as DCP for up to 33 days, absorption of calcium was 33 and 22% (respectively) at study Days 8/9 (Behling and Greger, 1988). Human subjects orally administered MCP showed a fractional absorption rate (as percent of administered dose) of 7.6% accompanied by only a slight increase in plasma calcium 1−3 hours after dosing (Schuette and Knowles, 1988). Studies conducted in animals have shown that calcium phosphates (administered as MCP or DCP) are most soluble in the acidic environment of the stomach; neutralization of pH in the intestines reduces the solubility and availability of calcium (or phosphate) in an absorbable form (To-o et al., 2003; Pak and Avioli, 1988; Schuette and Knowles, 1988; Shangraw, 1986). In addition, free phosphorus and calcium interact in the intestine to form calcium phosphate, reducing their absorption (EFSA, 2015).

Only a small fraction of phosphorus present in the blood is found complexed with calcium (as salts); of the phosphorus in the extracellular fluid, approximately one-third is complexed with calcium, magnesium, or sodium (EFSA, 2015). Data suggest that absorbed calcium and phosphorus are distributed to the tissues (ECHA, 2020a, b, c, d). Aged female rats administered 4- or 8-mg calcium/g diet as DCP for up to 33 days showed significant accumulation of calcium in the kidneys and phosphorus in the kidneys and tibias compared with other sources of calcium (dietary calcium or calcium magnesium chelate) (Behling and Greger, 1988). In bone, calcium and phosphorus are most commonly found complexed in the form of hydroxyapatite crystals; amorphous calcium phosphate is also observed (EFSA, 2015). In the kidney, interactions between phosphate and calcium occur such that phosphorus decreases urinary calcium excretion [as reviewed by EFSA (2015)]. Calcium and phosphorus are excreted in both the urine and feces (ECHA, 2020a, b, c, d). Numerous short-term studies of DCP or DCP dihydrate in the diet showed increased excretion of calcium and phosphorus in the feces and/or urine (Paßlack et al., 2016; Sprong et al., 2002; Govers et al., 1994).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

The database of oral toxicity studies in animals exposed to calcium phosphate salts is limited to a 28-day repeated-dose toxicity study and an R/D screening test of DCP [NIER (2010, 2009) as cited in OECD (2011a)], a combined short-term, repeated-dose with R/D toxicity study of TCP [NIER (2007) as cited in OECD (2012)], developmental toxicity studies of MCP monohydrate in rats, mice, and rabbits (FDRL, 1974), and a developmental toxicity study of a TCP food additive in rats (Güngörmüş et al., 2010). With exception of the latter study (Güngörmüş et al., 2010), these studies were unpublished and/or only available as reported in secondary sources (OECD, 2012, 2011a).

The study by Güngörmüş et al. (2010) is inadequate for deriving a provisional reference dose (p-RfD). The study identified increased transumbilical diameter and unilateral reductions in bone size as treatment-related effects; however, the study was confounded by several limitations. The study tested a TCP food additive that also contained significant microbiological and heavy metal contamination. In addition, the number of animals used per group was low (5/group), and only one dose level was used. Because it was not possible to determine whether observed effects were due to TCP exposure or other contaminants, effect levels were not identified for this study.

FDRL (1974) reported developmental toxicity studies of MCP monohydrate in rats, mice, and rabbits; however, this was an unpublished report containing appendices with minimal study details and some data tables (no measure of variation was provided, and no statistical analyses were performed). The studies by NIER (2007) as cited in OECD (2012) and NIER (2009, 2010) as cited in OECD (2011a) were conducted according to OECD guidelines and evaluated numerous systemic, reproductive, and developmental endpoints; however these studies were not published and are available only as reported in secondary sources. Given the limitations in the available studies for calcium phosphate salts, they were not considered suitable for deriving a p-RfD. However, the studies appear to provide sufficient data to develop a screening-level subchronic p-RfD value for calcium phosphate salts (see Appendix A).

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

Human and animal data are inadequate to derive subchronic or chronic provisional reference concentrations (p-RfCs) for calcium phosphate salts. No repeated-exposure inhalation data for calcium phosphate salts have been identified.

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 5 presents a summary of noncancer provisional reference values.

Table 5. Summary of Noncancer Reference Values for Calcium Phosphate Salts (Multiple CASRNs)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d) for calcium phosphate salts	Rat/both	No treatment-related effects	8×10^0	NOAEL	240	30	NIER (2007) as cited in OECD (2012); NIER (2009, 2010) as cited in OECD (2011a)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

HEC = human equivalent concentration; HED = human equivalent dose; 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 calcium phosphate salts. No human or animal studies evaluating cancer endpoints are available for any of the chemicals. Limited in vitro genotoxicity assays, available only in secondary sources (see Table 4A), 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 calcium phosphate salts is *"Inadequate Information to Assess Carcinogenic Potential"* for both the oral and inhalation routes of exposure.

Table 6. Cancer WOE Descriptor for Calcium Phosphate Salts (Multiple CASRNs)

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 calcium phosphate salts.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

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

3.5. DERIVATION OF CANCER RISK ESTIMATES

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

Table 7. Summary of Cancer Risk Estimates for Calcium Phosphate Salts (Multiple CASRNs)

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			

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

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for calcium phosphate salts. However, some information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of 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 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 the CPHEA.

DERIVATION OF SCREENING PROVISIONAL REFERENCE DOSES

As discussed in the main body of the report, the only available oral studies with adequate information to derive effect levels, NIER (2009, 2010) as cited in OECD (2011a), NIER (2007) as cited in OECD (2012), and FDRL (1974) were unpublished and/or available only as reported in secondary sources. However, these studies seem to have been well conducted and to provide adequate information for deriving a screening-level provisional toxicity value for calcium phosphate salts.

A no-observed-adverse-effect level (NOAEL) of 1,000 mg/kg-day is identified for dicalcium phosphate (DCP) in a 28-day repeated-dose toxicity study [NIER (2010) as cited in OECD (2011a)] and a reproductive/developmental (R/D) screening test [NIER (2009) as cited in OECD (2011a)], and for tricalcium phosphate (TCP) in a repeated-dose, with R/D toxicity, screening test [NIER (2007) as cited in OECD (2012)] based on the absence of any significant, treatment-related systemic, reproductive, or developmental effects at the highest tested dose. The FDRL (1974) study examined developmental toxicity in rats, mice, and rabbits, and did not observe biologically relevant effects at doses up to 465 mg MCP/kg-day. The lack of developmental effects observed for calcium phosphates is consistent with other inorganic phosphates. For example, developmental effects were not observed in rats treated with ammonium phosphates up to 1,500 mg/kg-day [Huntingdon (2002) as cited in OECD (2007) and ECHA (2002)]. Additionally, developmental effects were not observed in rats, rabbits, mice, or hamsters across multiple studies treated with sodium or potassium phosphates at doses up to 200 mg P/kg-day [e.g., Hodge (1964)], which is higher than the dose of 120 mg P/kg-day (monosodium phosphate) that caused increased incidence of nephrocalcinosis in rabbits (Ritskes-Hoitinga et al., 2004), indicating that systemic toxicity is more sensitive than developmental toxicity. Therefore, the NOAEL of 1,000 mg/kg-day identified for TCP and DCP is considered protective against potential reproductive and developmental toxicity because effects would most likely not have been observed in the FDRL (1974) study if the study authors had tested doses as high as 1,000 mg/kg-day. In the absence of any observed effects for calcium phosphates, these data were not amenable to benchmark dose modeling. Thus, after adjusting for human equivalent

dose, the NOAEL (HED)[2] of 240 mg/kg-day based on the animal dose of 1,000 mg/kg-day, is selected as the point of departure (POD).

Derivation of Screening Subchronic Provisional Reference Dose

A screening subchronic p-RfD of 8×10^0 mg calcium phosphate salt/kg-day is derived for calcium phosphate salts by applying a composite uncertainty factor (UF_C) of 30 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 3, and a database uncertainty factor [UF_D] of 3) to the selected POD of 240-mg DCP or TCP/kg-day (NOAEL [HED]), as follows:

Screening Subchronic p-RfD	=	NOAEL (HED) ÷ UF_C
	=	240 mg DCP or TCP/kg-day ÷ 30
	=	**8×10^0 mg calcium phosphate salt/kg-day**

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfD for calcium phosphate salts. Although the screening subchronic p-RfD is based on data for DCP and TCP, the value is expected to be protective for all calcium phosphates following application of a molecular weight adjustment and appropriate stoichiometric calculations. Studies of monocalcium phosphate (MCP) evaluating sensitive developmental endpoints identified only NOAELs at the highest doses tested. Although no repeated-dose data are available for calcium pyrophosphate (CPP), data from acute toxicity tests suggest that CPP is similar to or less toxic than other calcium phosphate compounds (likely owing to its lower solubility and resultant lower bioavailability relative to other calcium phosphate salts; see Table 1B and the "Acute Toxicity" sections). However, this screening subchronic RfD should not be applied to the risk assessment of magnesium phosphate salts, which is also a divalent inorganic phosphate, because there are no data with respect to the toxicity of magnesium phosphate salts relative to calcium phosphate salts.

[2]NOAEL (HED) = NOAEL (1,000 mg DCP or TCP) × DAF (0.24). The dosimetric adjustment factor (DAF) is calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Reference body weights for Sprague Dawley rats (average of males and females; 0.236 kg) and humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF. Reference body-weight data were used because study-specific data were not available (study summaries were obtained from secondary sources).

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfD for Calcium Phosphate Salts

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following calcium phosphates exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988).
UF_D	3	A UF_D of 3 is applied to account for deficiencies and uncertainties in the database because no subchronic or chronic-duration oral toxicity studies were identified. However, the database includes multiple R/D studies in various animal species (e.g., rats, mice, and rabbits) treated with various forms of calcium phosphates (e.g., DCP, MCP, and TCP) and repeated-dose toxicity studies up to 28 days.
UF_H	3	A UF_H of 3 is applied to account for human-to-human variability in susceptibility. Based on the comprehensive toxicity database for sodium and potassium phosphates, which included reproductive and developmental toxicity studies, the most sensitive toxicity effect after repeated oral exposure to phosphate is renal toxicity in animals, and the renal toxicity is also the most sensitive effect observed in susceptible humans after repeated exposure. An available animal study on DCP [NIER (2010) as cited in OECD (2011a)] has examined the most sensitive organ (i.e., kidneys). Therefore, the use of a NOAEL based on an animal study on DCP [NIER (2010) as cited in OECD (2011a)] which examined kidney effects as the POD will also protect against most sensitive kidney toxicity in susceptible human populations.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the subchronic POD is from 28-d repeated-dose and R/D screening studies for DCP and TCP.
UF_C	30	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

DAF = dosimetric adjustment factor; DCP = dicalcium phosphate; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; MCP = monocalcium phosphate; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; R/D = reproductive/developmental; TCP = tricalcium phosphate; 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.

Consideration of the Recommended Daily Intake

Phosphorus is an essential nutrient that exhibits a U-shaped dose-response curve: doses that are below physiological requirements may lead to deleterious effects, as can doses that exceed physiological requirements. The recommended daily intake (RDI) value for phosphorus is 700 mg phosphorus/day or 10 mg phosphorus/kg-day for a 70-kg adult (EFSA, 2015; IOM, 1997). However, the RDI includes phosphorus from less bioavailable and organic plant and animal sources in addition to inorganic phosphate sources. Furthermore, dietary intake of phosphorus in the U.S. population generally exceeds intake rates that are considered adequate. Using NHANES data between 2001 and 2014, McClure et al. (2017) estimated mean dietary phosphorus intake over the entire period to be 1,373 mg phosphorus/day (range of means by year was 1,324−1,414 mg phosphorus/day), or ~20 mg phosphorus/kg-day for a 70-kg adult. While little information regarding the proportion of total dietary phosphorus load from inorganic phosphate additives (the source most relevant to this assessment) was located, one source estimated the contribution to be ~500 mg phosphorus/day [Calvo and Uribarri (2013) as cited in Trautvetter et al. (2018)]. Given that the RDI of phosphorus includes both organic and inorganic

sources, and environmental exposure to inorganic phosphate will increase phosphorus intake over a dietary intake that exceeds adequate intake rates, the RDI is not considered to be a lower bound on the p-RfD for inorganic phosphates.

Derivation of Screening Chronic Provisional Reference Dose

There are no adequate subchronic or chronic-duration oral studies available for calcium phosphate salts; therefore, data are not adequate for derivation of a screening chronic p-RfD. It is not appropriate to use the NOAEL from the short-term and R/D studies that serve as the basis for the screening subchronic p-RfD to support derivation of a screening chronic p-RfD because it is based on a lack of significant biological effects. It is unknown whether exposure to that NOAEL value would result in adverse effects if exposure continued over a chronic duration.

APPENDIX B. DATA TABLES

Table B-1. Histopathological Kidney Effects in Parental Sprague Dawley Rats Administered TCP via Gavage during Premating, Mating, Gestation, and until Sacrifice (Males) or LD 4 (Females)[a]

Histopathological Effect	Dose in mg/kg-d					
	Main Study				Recovery	
	0	250	500	1,000	0	1,000
Males						
Tubular degeneration/regeneration						
Minimal	2/5 (40)[b]	1/5 (20)	1/5 (20)	2/5 (40)	1/5 (20)	4/5 (80)
Slight	0/5 (0)	1/5 (20)	1/5 (20)	3/5 (60)	0/5 (0)	0/5 (0)
Total	2/5 (40)	2/5 (40)	2/5 (40)	5/5 (100)	1/5 (20)	4/5 (80)
Females						
Mineralization						
Minimal	4/5 (80)	5/5 (100)	2/5 (40)	2/5 (40)	2/5 (40)	2/5 (40)
Slight	0/5 (0)	0/5 (0)	2/5 (40)	2/5 (40)	0/5 (0)	1/5 (20)
Total	4/5 (80)	5/5 (100)	4/5 (80)	4/5 (80)	2/5 (40)	3/5 (60)

[a]NIER (2007) as cited in OECD (2012); no significant changes from control based on Fisher's exact test (one-sided $p < 0.05$) conducted for this review.
[b]Values denote number of animals showing changes ÷ total number of animals examined (percent incidence).

LD = lactation day; TCP = tricalcium phosphate.

Table B-2. Developmental Effects in Dutch Belted Rabbits Administered MCP Monohydrate via Gavage on GDs 6−18[a]

Parameters	Dose in mg/kg-d					
	MCP monohydrate					6-AN
	0	2.17	10.10	46.7	217	2.5
Number pregnant[b]	12/21 (57)	12/21 (57)	17/27 (63)	10/15 (67)	10/27 (37)	9/18 (50)
Mortality prior to GD 29[b]	2/12 (17)	1/12 (8)	4/17 (24)	0/10 (0)	0/10 (0)	0/9 (0)
Total litter loss[b]	0/10 (0)	1/11 (9)	0/13 (0)	1/10 (10)	2/10 (20)	1/9 (11)
Number of corpora lutea/doe[c, d]	11.4 ± 5.45 (14)	9.43 ± 3.81 (14) [−17][d]	9.55 ± 3.26 (20) [−16]	8.46 ± 2.02 (13) [−26]	6.37 ± 5.40* (19) [−44]	9.75 ± 5.61 (12) [−14]
Number of implant sites/doe[c, d]	5.80 ± 1.40 (10)	5.64 ± 2.01 (11) [−3]	6.08 ± 2.02 (13) [+5]	5.00 ± 1.79 (10) [−14]	4.90 ± 1.97 (10) [−16]	6.33 ± 2.31 (9) [+9]
Number of live fetuses[c, d]	5.10 ± 2.10 (10)	4.45 ± 2.54 (11) [−13]	5.85 ± 2.21 (13) [+15]	4.30 ± 2.15 (10) [−16]	4.50 ± 2.62 (10) [−12]	5.44 ± 2.45 (9) [+7]

[a]FDRL (1974).
[b]Values denote number of animals showing changes ÷ total number of animals examined (percent incidence).
[c]Data are means ± SD (*n*); SDs were calculated for this review based on raw data provided in the study.
[d]Percentage value in brackets is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by *t*-test (two-tailed; $p < 0.05$) conducted for this review.

6-AN = 6-aminonicotinamide; GD = gestation day; MCP = monocalcium phosphate; SD = standard deviation.

Table B-3. Developmental Effects in Wistar Rats Administered TCP via Gavage on GDs 0−20[a]

Parameters	Dose in mg/kg-d		
	0 (untreated control)	**0 (vehicle control)**	**175**
Weight of placenta (g)	0.45 ± 0.0007[b]	0.44 ± 0.03	0.40 ± 0.0006* (−11) [c]
Transumbilical diameter (mm)	21.27 ± 0.38	22.41 ± 0.44	24.24 ± 0.45*, † (+8)
Skull; diameter of *y*-axis (mm)	11.01 ± 0.24	10.55 ± 0.29	9.65 ± 0.46* (−9)
Left ulna (mm)	2.30 ± 0.08	2.33 ± 0.05	1.65 ± 0.20*, † (−29)
Right ulna (mm)	2.38 ± 0.11	2.34 ± 0.06	1.77 ± 0.20 (−24)
Left femur (mm)	1.66 ± 0.11	1.52 ± 0.05	1.08 ± 0.13*, † (−29)
Right femur (mm)	1.71 ± 0.14	1.52 ± 0.13	1.20 ± 0.11 (−21)

[a]Güngörmüş et al. (2010).
[b]Data are means ± SE.
[c]Value in parentheses is percent change relative to vehicle-only control = [(treatment mean − vehicle control mean) ÷ vehicle control mean] × 100.
*Significantly different from untreated control ($p < 0.05$), as reported by the study authors.
†Significantly different from vehicle control ($p < 0.05$), as reported by the study authors.

GD = gestation day; SE = standard error; TCP = tricalcium phosphate.

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