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Provisional Peer-Reviewed Toxicity Values for

Sodium and Potassium 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 SODIUM AND POTASSIUM 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 eComments Chemical Safety website at https://ecomments.epa.gov/chemicalsafety/.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV 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

In deriving provisional reference doses (p-RfDs) for sodium and potassium (Na/K) salts of inorganic phosphates, two notable departures from the traditional approach to contaminants found on contaminated sites exist: (1) the background concentrations found in humans is not zero, and (2) the background concentrations found in contaminated sites is not zero. As discussed below, phosphorus, an essential nutrient commonly found in various phosphates, exhibits a "U-shaped" dose-response curve, wherein doses above deficiency and doses below toxicity may overlap for some population subgroups. Thus, care must be taken in the interpretation and risk communication of extra-dietary exposures above those occurring in a standard American diet that may result from exposures at contaminated sites.

Phosphorus (P) is most commonly found in nature in its pentavalent form in combination with oxygen, known as phosphate or orthophosphate anion (PO_4^{3-}). Phosphorus is an essential constituent of all living organisms, and its content is quite uniform across most plant and animal tissues. Orthophosphoric acid (H_3PO_4) is the basic unit for all phosphates. Condensed (oligo-, pyro-, meta-, and other polyphosphates) are formed when two or more orthophosphoric acid molecules condense into a single molecule. Pyrophosphates refer to compounds with two condensed orthophosphates $(P_2O_7)^{4-}$, and higher number polymers are termed polyphosphates, sometimes followed by a suffix indicating the number (e.g., $[HPO_3]_n$; thus, 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 polyphosphate anions) can be grouped into classes on the basis of their cations: monovalent cations (sodium [Na^+], potassium [K^+], ammonium [NH_4^+], and hydrogen [H^+]); bivalent calcium (Ca^{2+}) and magnesium (Mg^{2+}); and trivalent aluminum (Al^{3+}). The phosphoric acids have been grouped with the other monovalent cations on the basis of valence state of the cation.

Organic phosphates are commonly found in the form of esters as nucleotides or deoxynucleotides (e.g., adenosine monophosphate [AMP], adenosine diphosphate [ADP], adenosine triphosphate [ATP], or deoxyadenosine triphosphate [dATP]) and in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Free orthophosphate anions can be released by the hydrolysis of the phosphoanhydride bonds in ATP or ADP. These phosphorylation and dephosphorylation reactions are the immediate storage and source of energy for many metabolic processes. ATP and ADP are often referred to as high-energy phosphates, as are the phosphagens in muscle tissue. Similar reactions exist for the other nucleoside diphosphates and triphosphates. Various other organic phosphates, such as phosphoproteins, are important in kinase cascades in signal transduction pathways, structurally as phospholipids, or as sugar-phosphates in intermediary metabolism. Plants also contain poorly absorbed phytates (inositol hexaphosphates), which are storage forms of phosphorus principally found in seeds.

This document addresses the available data on the toxicity of phosphoric acids and monovalent (sodium and potassium) salts of inorganic phosphates (see Table 1A). Aluminum, ammonium, and the divalent salts (calcium [Ca] and magnesium) are not included in this assessment because they are expected to have differing toxicity, chemistry, or toxicokinetics.

Specifically, ammonium ions are expected to exert toxic effects that are independent of the monohydrogen phosphate moiety, which would confound the hazard identification for other inorganic phosphates. In addition, ammonium phosphates exhibit different chemistry and different toxicity than Na/K phosphates: the ammonium salts are relatively unstable because ammonium hydroxide is a weaker base than metal hydroxides and ammonia can escape as a gas (Gard, 2005). Ca phosphates are much less soluble than sodium or potassium phosphates (Gard, 2005). In addition, interactions between phosphate and Ca occur both in the intestine and in the kidney. In the intestines, the phosphate ion present will transition from the monovalent dihydrogenphosphate in areas near the stomach to the divalent hydrogen phosphate ion as the pH of the intestinal contents approaches pH 7 (where calcium phosphate formation reduces absorption of both nutrients) and in the kidney (where phosphate decreases urinary Ca excretion) [as reviewed by EFSA (2015)]. These interactions do not occur with monovalent (sodium and potassium) phosphates. There is evidence that the ratio of calcium:phosphate is an important determinant of phosphate toxicity (particularly regarding bone health); thus, administration of calcium phosphate is expected to yield different toxicological effects than would administration of sodium or potassium phosphate. Finally, although magnesium phosphates are somewhat more soluble than calcium phosphates (Gard, 2005), both are most appropriately considered with other divalent salts.

Na/K salts of inorganic phosphates are used in a wide variety of applications; a few examples include in fertilizers, soaps, detergents, pH-regulating agents, antifreezing agents, adsorbents in baking powders, food nutrient supplements, and acid cleansers; in electroplating, dyeing and tanning, wastewater treatment, pottery glazing, and soldering and brazing; as a scale inhibitor in boiling water treatment; and as a fireproofing agent (NLM, 2021; OECD, 2009). In general, Na/K salts of inorganic phosphates are soluble in water (see Table 1B), and the phosphate moiety may persist indefinitely in natural waters (NLM, 2021). Polyphosphates decompose ultimately to orthophosphate in water, sodium tripolyphosphate ($Na_5P_3O_{10}$) hydrolyzes to phosphonic acid (H_2PO_3), and tetrasodium phosphate ($Na_4P_2O_7$) slowly hydrolyzes to orthophosphate (NLM, 2021). Sodium polyphosphates ($[NaPO_3]_n$) and sodium hexametaphosphate ($[NaPO_3]_6$) depolymerize in aqueous solution to form sodium trimetaphosphate ($[NaPO_3]_3$) and sodium orthophosphates (NLM, 2021; CIR Expert Panel, 2016).

Human exposure to Na/K salts of inorganic phosphates is likewise ubiquitous, particularly through their use as food additives and in water treatment. Although little information was located regarding the proportion of total dietary P load from monovalent salts of inorganic phosphate additives, one source estimated the contribution as ~500 mg P/day (Calvo and Uribarri, 2013 as cited in Trautvetter et al., 2018). Phosphate blends, which may include any of the compounds in Table 1A, are also used in municipal water treatment for a variety of purposes, including to control scale and corrosion; to reduce iron, lead, and copper concentrations in drinking water; and to reduce staining, scale, and objectionable tastes and odors (Willhite et al., 2013); human exposure may occur through any of these uses. Application of monovalent salts of inorganic phosphates in fertilizers and use in consumer products, such as toothpaste, water softeners, and detergents, also provide opportunities for human exposure. Finally, sodium phosphate (typically as a mixture of mono- and disodium phosphate) has been used as a bowel cleansing agent for colonoscopy preparation and as a therapeutic treatment for constipation. Its use in bowel cleansing was significantly curtailed by the U.S. Food and Drug Administration (FDA) in 2008 in response to adverse event reports (FDA, 2008).

The empirical formulas for selected Na/K salts of inorganic phosphates are shown in Table 1A. Tables 1A and 1B show the nomenclature and physicochemical properties (respectively) of the selected salts.

Table 1A. Nomenclature, Chemical Formula, and Molecular Weight of Selected Na/K Salts of Inorganic Phosphates

Compound	CASRN	Empirical Formula	MW (g/mol)[a]	MW Ratio P: Compound[b]	Physical State[a]
Orthophosphoric acid	7664-38-2	H_3PO_4	97.995	0.31608	Colorless crystals or viscous liquid
Polyphosphoric acid	8017-16-1	$(HPO_3)_n$; molecular weights vary			Clear, viscous liquid
Sodium dihydrogen orthophosphate (monosodium phosphate)	7558-80-7	NaH_2PO_4	119.977	0.25817	White or colorless crystalline powder
Sodium monohydrogen orthophosphate (disodium phosphate)	7558-79-4	Na_2HPO_4	141.96	0.21819	Colorless crystals or white hygroscopic powder
Sodium orthophosphate (trisodium phosphate)	7601-54-9	Na_3PO_4	163.94	0.18893	Colorless crystals
Sodium dihydrogen pyrophosphate (disodium diphosphate)	7758-16-9	$Na_2H_2P_2O_7$	221.94	0.27912	White crystalline powder
Sodium pyrophosphate (tetrasodium diphosphate)	7722-88-5	$Na_4P_2O_7$	265.94	0.23294	Colorless transparent crystals or white powder
Sodium tripolyphosphate (pentasodium triphosphate)	7758-29-4	$Na_5P_3O_{10}$	367.86	0.25260	White powder
Sodium trimetaphosphate	7785-84-4	$(NaPO_3)_3$	305.882[d]	0.30378	White crystals or white crystalline powder[c]
Sodium polyphosphate	68915-31-1	$(NaPO_3)_n$, where n = 10−15; molecular weights vary			Clear hygroscopic glass
Sodium hexametaphosphate	10124-56-8	$(NaPO_3)_6$	611.763	0.30378	Clear hygroscopic glass
Potassium dihydrogen phosphate (monopotassium phosphate)	7778-77-0	KH_2PO_4	136.085	0.22761	Colorless crystals or white granular powder
Potassium monohydrogen phosphate (dipotassium phosphate)	7758-11-4	K_2HPO_4	174.18	0.17783	White crystals or colorless granules or powder
Potassium phosphate (tripotassium phosphate)	7778-53-2	K_3PO_4	212.265[d]	0.14389	Colorless or white hygroscopic crystals or granules[d]
Potassium pyrophosphate (tetrapotassium diphosphate)	7320-34-5	$K_4P_2O_7$	330.33[c]	0.18753	Colorless crystals or white, very hygroscopic powder[d]

Table 1A. Nomenclature, Chemical Formula, and Molecular Weight of Selected Na/K Salts of Inorganic Phosphates

Compound	CASRN	Empirical Formula	MW (g/mol)[a]	MW Ratio P: Compound[b]	Physical State[a]
Potassium tripolyphosphate (pentapotassium triphosphate)	13845-36-8	$K_5P_3O_{10}$	448.403[d]	0.20723	White, very hygroscopic powder or granules[d]

[a]NLM (2021) unless otherwise specified.
[b]MW of P = 30.974 g/mol (NLM, 2021).
[c]CIR Expert Panel (2016).
[d]PubChem (2018).

MW = molecular weight; Na/K = sodium and potassium; P = phosphorus.

Table 1B. Physicochemical Properties of Selected Na/K Salts of Inorganic Phosphates[a, b]

Compound	Chemical Formula	Melting Point (°C)	Density (g/cm^3 at 25°C)	pH (unitless)	pKa (unitless)	Solubility in Water (mg/L at 25°C)
Orthophosphoric acid	H_3PO_4	42.4	1.87	1.5 (0.1 N aqueous solution)	pK_1 = 2.15, pK_2 = 7.09, pK_3 = 12.32	5.48×10^6 at 20°C
Polyphosphoric acid	$(HPO_3)_n$	Varies				Soluble
Sodium dihydrogen orthophosphate (monosodium phosphate)	NaH_2PO_4	200 (decomposes)	2.36	4.5 (1% aqueous solution)	6.8−7.2	9.49×10^5
Sodium monohydrogen orthophosphate (disodium phosphate)	Na_2HPO_4	35 (dodecahydrate)	1.7 (approximate)	9.1 (1% aqueous solution at 25°C)	pK_1 = 2.15	1.18×10^5
Sodium orthophosphate (trisodium phosphate)	Na_3PO_4	1,583 (anhydrous)[b] 75 (dodecahydrate)[c]	2.54	11.5−11.9 (0.1−1% solution)	NV	1.45×10^5
Sodium dihydrogen pyrophosphate	$Na_2H_2P_2O_7$	220 (decomposes)	1.86 (hexahydrate)	NV	NV	3.5×10^5 at 40°C
Tetrasodium pyrophosphate (tetrasodium diphosphate)	$Na_4P_2O_7$	988 (anhydrous) 79.5 (decahydrate)[c]	2.534	10.2 (1% solution)	NV	6.7×10^4
Sodium tripolyphosphate (pentasodium triphosphate)	$Na_5P_3O_{10}$	622	NV	9.7−9.8 (1% solution at 25°C)	NV	2.0×10^5

Table 1B. Physicochemical Properties of Selected Na/K Salts of Inorganic Phosphates[a, b]

Compound	Chemical Formula	Melting Point (°C)	Density (g/cm^3 at 25°C)	pH (unitless)	pKa (unitless)	Solubility in Water (mg/L at 25°C)
Sodium trimetaphosphate	$(NaPO_3)_3$	53 (hexahydrate)	1.786 (hexahydrate)	NV	NV	2.2×10^5
Sodium polyphosphate	$(NaPO_3)_n$	Varies				Soluble in water[d]
Sodium hexametaphosphate	$(NaPO_3)_6$	628	NV	NV	NV	Slowly soluble in water
Potassium dihydrogen orthophosphate (monopotassium phosphate)	KH_2PO_4	253	2.34	4.4–4.7	NV	2.5×10^5
Potassium monohydrogen orthophosphate (dipotassium phosphate)	K_2HPO_4	NV/decomposes	0.6 to ~0.7[e]	8.8 (1% solution)	NV	1.68×10^6
Potassium phosphate (tripotassium phosphate)	K_3PO_4	NV	NV	11.5–12.3 (1% solution)[f]	NV	Freely soluble in water[f]
Tetrapotassium pyrophosphate (tetrapotassium diphosphate)	$K_4P_2O_7$	1,090	NV	10.0–10.8 (1% solution)[f]	NV	1.87×10^6 [f]
Potassium tripolyphosphate (pentapotassium triphosphate)	$K_5P_3O_{10}$	NV	NV	9.2–10.5 (1% solution)[f]	NV	Very soluble in water[f]

[a]Octanol-water partition coefficient, Henry's law constant, soil adsorption coefficient, atmospheric OH rate constant, and atmospheric half-life are not applicable to inorganic phosphates.
[b]NLM (2021), unless otherwise specified.
[c]U.S. EPA (2012).
[d]CIR Expert Panel (2016).
[e]OECD (2006), potassium.
[f]PubChem (2018).

Na/K = sodium and potassium; NV = not available; pKa = acid dissociation constant.

A summary of available subchronic and chronic toxicity values for phosphorus from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Subchronic or Chronic Toxicity Values and Adequate Intake Values for Na/K Salts of Inorganic Phosphates (Multiple CASRNs)

Source (parameter)[a, b]	Phosphorus Form	Value (applicability)	Notes	Reference[c]
Noncancer				
IRIS (RfC)	Phosphoric acid (PA)	0.01 mg/m^3	Basis: Bronchiolar fibrosis in a 13-wk rat study. This RfC is for aerosols of PA and P oxidation products and does not apply to elemental P or other forms of P, such as phosphorus salts.	U.S. EPA (1995)
HEAST	NA	NV	NA	U.S. EPA (2011a)
DWSHA	NA	NV	NA	U.S. EPA (2018)
ATSDR	NA	NV	NA	ATSDR (2018)
EFSA (AI)	P	AI by age: 7−11 mo: 200 mg/d 1−3 yr: 300 mg/d 4−10 yr: 600 mg/d 11−17 yr: 800 mg/d Adults and pregnant/lactating women: 700 mg/d	Phosphorus from all sources, expressed as P.	EFSA (2015)
IOM (UL)	P	Children: 3,000 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)
WHO (MTDI)	P	70 mg/kg	Maximum intake of P across all sources; based on nephrocalcinosis in rats.	WHO (1982)
CalEPA (REL, chronic inhalation)	PA	7 µg/m^3	Basis: Bronchiolar fibrosis in rats.	CalEPA (2017, 2008)
OSHA (PEL)	PA	1 mg/m^3	8-h TWA for general industry, construction, and shipyard employment.	OSHA (2020, 2017a, 2017b)
NIOSH (REL)	PA	1 mg/m^3	TWA for up to a 10-h workday during a 40-h workweek.	NIOSH (2016)
ACGIH (TWA-TLV)	PA	1 mg/m^3	Basis: Upper respiratory tract, eye, and skin irritation.	ACGIH (2016)
USAPHC (air-MEG)	PA	1-yr negligible: 0.068 mg/m^3	Based on IRIS.	U.S. APHC (2013)

Table 2. Summary of Available Subchronic or Chronic Toxicity Values and Adequate Intake Values for Na/K Salts of Inorganic Phosphates (Multiple CASRNs)

Source (parameter)[a, b]	Phosphorus Form	Value (applicability)	Notes	Reference[c]
USAPHC (soil-MEG)	PA	1-yr negligible: 1,000,000 mg/kg	Basis: Noncancer.	U.S. APHC (2013)
Cancer				
IRIS	NA	NV	NA	U.S. EPA (2020)
HEAST	NA	NV	NA	U.S. EPA (2011a)
DWSHA	NA	NV	NA	U.S. EPA (2018)
NTP	NA	NV	NA	NTP (2016)
CalEPA	NA	NV	NA	CalEPA (2020, 2019)
ACGIH	NA	NV	NA	ACGIH (2020)

[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; IOM = Institute of Medicine; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; 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; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; TLV = threshold limit value; TWA = time-weighted average; UL = tolerable upper intake level.
[c]Reference date is the publication date for the database and not the date the online source was accessed.

NA = not applicable; Na/K = sodium and potassium; NV = not available; P = phosphorus; PA = phosphoric acid.

Non-date-limited literature searches were conducted in October 2017 and updated most recently in February 2022 for studies relevant to the derivation of provisional toxicity values for inorganic phosphates, including phosphoric acid (PA) and selected Na/K salts (names and CASRNs shown in Table 1A). The literature search updated conducted in February 2022, post External Peer Review, did not identify any studies which would affect the quantitative conclusions of the PPRTV assessment.

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 (including TSCATS1), and Web of Science. Secondary key words were applied in EndNote to help prioritize results for screening. EndNote was used to manually screen items published since the previous version of this PPRTV in 2009. Studies were then imported into SWIFT Review software to identify those references most likely to be applicable to a human health risk assessment, and resulting studies were imported to EndNote. In brief, SWIFT Review has preset literature search strategies ("filters") developed by information specialists that can be applied to identify studies that are more likely to be useful for identifying human health content

from those that likely do not (e.g., environmental fate). Only studies meeting the populations, exposures, comparators, and outcomes (PECO) criteria are cited. The following databases 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), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Pesticide Information Retrieval System (NPIRS), National Toxicology Program (NTP), Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database, OECD Screening Information Data Set (SIDS) High Production Volume Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

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 Na/K salts of inorganic phosphates, and include selected potentially relevant acute, short-term, subchronic, and chronic studies as well as reproductive and developmental toxicity studies. These tables include studies for which no-observed-adverse-effect levels (NOAELs)/lowest-observed-adverse-effect levels (LOAELs) could be identified (principal study is identified in bold). All NOAELs/LOAELs were identified by the U.S. EPA unless noted otherwise. Studies that could not be used quantitatively (for various reasons such as study quality issues, form of P not specified, Ca intake not measured, etc.) but may be useful for hazard identification, are presented in Tables 4–10. 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 Na/K Salts of Inorganic Phosphates (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)				
Acute	Retrospective cohort study of 9,799 patients given OSP or PEG purgative prior to endoscopy, who had available serum CR levels within 1 yr of the procedure.	0 (PEG), 164	Use of an OSP purgative was associated with increased odds of acute kidney injury (OR = 2.35, 95% CI = 1.51−3.66) compared with use of PEG purgative.	NDr	164	Hurst et al. (2007); same LOAEL as FDA (2008) warning	PR
Acute	Male and female children (>5 yr old) or adults exposed for 1−3 d to 1,220−7,340 mg P/d for constipation relief.	40−105	Dose above which dehydration, electrolyte imbalances, and renal and cardiovascular effects that are fatal in some cases have occurred.	NDr	40	FDA (2014)	PR
Acute	16 M/0 F, meal containing supplement, three different meals (1 wk between meals) containing 400, 800, or 1,200 mg P; breakfasts and dinners on these days each contained 400 mg P/meal. Participants served as their own controls. Total intake: 1,200, 1,600, or 2,000 mg P/d on 1 d.	19.87, 26.49, or 33.11 (including diet)	Significantly decreased percent FMD, a measure of endothelial function) at 1, 2, and 4 h after the 800 and 1,200 mg P test meals; no difference in percent FMD 20 h after the meal. Blood pressure and other serum chemistry measures were not affected by treatment.	19.87	26.49	Nishi et al. (2015)	PR
Acute	11 healthy male volunteers, mean age 24.6 yr; double-blinded crossover design. Participants consumed a single meal containing either 400 or 1,200 mg P (supplemental P provided as neutralized phosphate supplement). Intake at other meals was not reported. Participants served as their own controls.	6.62 or 19.87	Percent FMD was significantly decreased, and serum P was significantly increased 2 h after the high-dose meal (compared with premeal measures); FMD returned to normal within 24 h. Blood pressure and other serum chemistry measures were not affected by treatment.	NDr	19.87	Shuto et al. (2009)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
Short-term	31 adults (21 M and 10 F) mean age 66.0 yr with early CKD (eGFR ≥45 mL/min/1.73 m^2 and urine albumin:creatinine ratio ≥17 mg/g in men or 25 mg/g in women); randomized double-blind crossover trial. Supplemental P given as commercial diet soda or breakfast bars.	15.38 or 24.87	No effect on frequency of self-reported GI symptoms. Intake of P additives did not significantly alter urinary albumin or serum P or FGF-23. Blood pressure was not altered by exposure.	24.87	NDr	Chang et al. (2017)	PR
Short-term	10 healthy women aged 23−29 yr, mean body weight of 60 kg, with typical P intakes between 1,060 and 1,810 mg P/d based on 14-d dietary records; crossover design. After a 4-wk control period (with mean intakes of 1,700 mg P/d and 1,500 mg Ca/day), participants were given sodium phosphate (NaH_2PO_4) tablets (containing 620 mg P) and orange juice containing 975 mg P (bringing their total daily intake to 3,008 mg P) for 6 wk; this period was followed by a 4-wk washout period in which intakes were similar to the control period.	28.33 (control period) or 50.13 (including diet)	Participants reported diarrhea, soft stools, and intestinal disturbances (not further described) during supplementation.	NDr	50.13	Grimm et al. (2001)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
Short-term	43 (35F/8M) patients with irritable bowel syndrome-constipation predominant; recruited by researchers who were also gastroenterologists; open-label dose ranging study. Patients were divided in two groups. Group A had a mean age of 46 yr, while Group B had a mean age of 49 yr. Group A was 15 F/3 M, while group B was 20 F/5 M. Mean body weights were 155 (70.4 kg) lb for Group A and 162 lb (73.6 kg) for Group B. Supplemental P provided as sodium phosphate, 1.5 g tablets, (sodium phosphate (NaH_2PO_4) and disodium phosphate (Na_2HPO_4) in a ratio of 2.67:1)	Approximate doses were 855 mg P (25.2 mg P/kg-d) or 1.770 g P (48.2 g P/kg-d), but patients were allowed to increase or decrease dose based on symptoms. High dose group (eight tablets) received 3.44 g P/d	Symptoms reported in the low-dose group included nausea, diarrhea, and incomplete evacuation (1/18 each). In the high-dose group, nausea and diarrhea were reported by 4/25 and 3/25, respectively, and additional symptoms included bloating (2/25) and cramping, headache, lower back pain, migraine, and lower quadrant pain (1/25 each). No effects on body weight, heart rate, or blood pressure were observed. The only serum chemistry change that was considered noteworthy and related to treatment was occasional hypokalemia in five patients (in both dose groups). The study authors concluded that the low dose was well tolerated and suggested that a starting dose of 2−4 tablets/d (equivalent to 885−1,770 mg P/d) would be appropriate.	25.2	48.1	Medoff et al. (2004)	PR
2. Inhalation (mg/m^3)							
ND							

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
Animal							
			1. Oral (mg/kg-d)				
Subchronic	10 M/0 F per dose group, Wistar rat, 0.6 (as $CaHPO_4$), 1.2, or 1.8% P (as $CaHPO_4$ and KH_2PO_4) in diet for 8 wk.	510 (referent), 980, or 1,400	Statistically significantly decreased body weight (11% less than control at the end of exposure) and food intake; significantly decreased bmc and bmd; alterations in several measures of bone histomorphometry; nonsignificant decrease in bone strength.	NDr	980	Huttunen et al. (2007)	PR
Subchronic	0 M/5 F per dose group, Wistar rat, 0.5, 1.5% P (as KH_2PO_4) in diet for 6 wk.	270 (referent) or 800	Significantly decreased bmd, significantly increased serum osteocalcin, and urinary deoxypyridinoline.	NDr	800	Koshihara et al. (2005)	PR
Subchronic	0 M/6−16 F per dose group, Wistar RIV:TOX rat, 0.4 or 0.6% P (as NaH_2PO_4 dihydrate) in diet for 4 wk.	390 (referent) or 580 (Experiment 1); 410 (referent) or 580 (Experiment 2)	Renal effects (increased urinary albumin, increased relative kidney weight, and nephrocalcinosis).	NDr	580	Ritskes-Hoitinga et al. (1989)	PR
Subchronic	**8 M/0 F per dose group, NZW rabbit, 0.45 or 0.88% P (as NaH_2PO_4 dihydrate) in diet for 8 wk.**	**150 (referent) or 290**	**Nephrocalcinosis, based on significantly increased kidney Ca (and P), and significantly increased severity scores for cortical calcifications.**	**NDr**	**290**	**Ritskes-Hoitinga et al. (2004)**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
Subchronic	6 M/0 F per dose group, Wistar rat, 0.3, 0.6, 0.9, 1.2, or 1.5% P (as KH_2PO_4) in diet for 4 wk.	250 (referent), 450, 670, 920, or 1,000	Decreased body-weight gain and body-weight gain normalized to intake (decreased 38 and 26% relative to comparison group, respectively). Renal Npt IIa mRNA and brush border protein decreased at high dose.	920	1,000	Tani et al. (2007)	PR
Subchronic	6 M/0 F per dose group, Sprague Dawley rat, 0.6 or 1.2% P (as KH_2PO_4) in diet for 4 or 14 wk.	530 (referent) or 1,100	Decreased terminal body weight (~14% less than control; shown graphically) after 14 wk; decreased visceral fat mass and plasma leptin, and increased serum BUN and absolute kidney weights (~12% higher than comparison group; shown graphically) after 4 wk.	NDr	1,100	Abuduli et al. (2016)	PR
Subchronic	20 M/20 F, Birmingham-Wistar rat, control and 3% (526 or 1,650 mg P/100 g) diet (as Tetron K, analyzed as 97.5% $Na_4P_2O_7$ and 2.5% Na_3PO_4) in diet for 16 wk. Additional dose groups were reported, but without P content of the diet, precluding dose estimation.	280 (referent) or 860 (M); 350 (referent) or 1,100 (F)	Decreased body-weight gain (females); increased relative heart, stomach and kidney weights (both sexes); increased relative testes weight (males) and increased relative intestine weight (females); impaired kidney function (concentration test, both sexes) at 860 or 1,100 mg P/kg-d. Increased relative kidney weight, renal histopathology, and impaired kidney function (males) also occurred in animals receiving intermediate doses for which the analytical P concentrations were not given. For this reason, effect levels could not be determined.	NDr	NDr	Datta et al. (1962)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
Subchronic	20 M/20 F, Birmingham-Wistar rat, control (referent) and 5% (526 or 1,598 mg P/100 g diet (as Na_2HPO_4) in diet for 16 wk.	280 (referent) or 840 (M); 350 (referent) or 1,000 (F)	Increased relative kidney weight (17 and 39% in males and females, respectively); impaired kidney function (concentration test, both sexes); and increased incidence of renal histopathology (medullary calcification and necrosis; tubular casts; hemorrhages/exudate; chronic inflammatory changes).	NDr	840	Datta et al. (1962)	PR
Subchronic to chronic	12 M/0 F, Wistar rat, 0.43 or 1.3% P in diet (as K_2HPO_4) or 0.46 or 1.2% P in diet (as $[NaPO_3]_6$) for 60 or 150 d (8.5 or 21 wk).	380 (referent) or 1,100 (K_2HPO_4); 400 (referent) or 1,100 ($[NaPO_3]_6$)	There was a 12% increase in body weight gain in the high K_2HPO_4 group and in the high $(NaPO_3)_6$ group; relative testes weight was increased by 11% compared with the low $(NaPO_3)_6$ group.	1,100	NDr	Dymsza et al. (1959)	PR
Chronic	No studies met inclusion criteria[d].						
Reproductive	No studies met inclusion criteria[d].						
Developmental	No studies met inclusion criteria[d].						

Table 3A. Summary of Potentially Relevant Noncancer Data for Na/K Salts of Inorganic Phosphates (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]
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: All doses are reported in mg P/kg-day. Doses are presented as ADDs in (mg P/kg-day) units for oral noncancer effects.
[c]Notes: PR = peer reviewed; PS = principal study.
[d]Inclusion criteria are detailed in the text. Studies that did not meet inclusion criteria are considered supporting data and discussed briefly in the text or presented in tables.

ADD = adjusted daily dose; bmc = bone mineral content; bmd = bone mineral density; BUN = blood urea nitrogen; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; CR = creatinine; eGFR = estimated glomerular filtration rate; F = female(s); FGF-23 = fibroblast growth factor-23; FMD = flow mediated dilation; GI = gastrointestinal; KH_2PO_4 = monopotassium phosphate; K_2HPO_4 = dipotassium phosphate; LOAEL = lowest-observed-adverse-effect level; M = male(s); mRNA = messenger ribonucleic acid; $(NaPO_3)_6$ = sodium hexametaphosphate; Na/K = sodium and potassium; Na_2HPO_4 = disodium phosphate; Na_3PO_4 = sodium orthophosphate; $Na_4P_2O_7$ = sodium pyrophosphate; NaH_2PO_4 = monosodium phosphate; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NPT Iia = type II sodium-dependent phosphate transporter; NZW = New Zealand White; OR = odds ratio; OSP = oral sodium phosphate; P = phosphorus; PEG = polyethylene glycol.

Table 3B. Summary of Potentially Relevant Cancer Data for Na/K Salts of Inorganic Phosphates (Multiple CASRNs)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/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 data pertinent to the hazard assessment of oral exposure to monovalent inorganic phosphates can be grouped into three main categories: human epidemiological studies on associations between dietary P intake and health outcomes, randomized controlled trials of humans exposed to Na/K salts of inorganic phosphates for acute or short-term durations, and human studies of renal toxicity or gastrointestinal (GI) symptoms after acute exposure to oral sodium phosphate (OSP; a combination of monosodium phosphate and disodium phosphate) for bowel cleansing or constipation treatment.

The database of human studies for oral exposure to P and monovalent inorganic phosphates is extensive. To select the studies most relevant to the assessment of inorganic phosphate toxicity, and particularly for dose-response assessment, several overall criteria were established:

- Human studies published before the comprehensive IOM (1997) review were excluded, as these studies would have been considered in establishing the recommended daily intake (RDI) and tolerable upper intake levels (UL) derived at that time. Due to lack of suitable dose-response data to derive tolerable upper intakes directly, the Institute of Medicine (IOM) instead used the high end of the normal adult serum P range as the basis for the dietary UL of 4 g P/day for adults and 3 g P/day for adults >70 years old (12.5 and 9.4 g/d respectively, as monohydrogen phosphate).
- Studies that did not explicitly report an administered dose or estimated intake of phosphate were excluded. This group included studies of dietary intake that reported exposure qualitatively (e.g., high, medium, low) and therefore could not be used for dose-response assessment.
- Studies that used serum P, urinary P, or another potential marker (such as parathyroid hormone [PTH]) to assess exposure were not included as they are not considered a reliable measure of phosphate exposure or intake [as reviewed by EFSA (2015)], as both absorption and excretion of P are tightly regulated in the human body by homeostatic mechanisms (see further discussion in Section 2.3.3).
- Abstracts of conference presentations or posters, correspondence, and foreign language studies were excluded, unless they identified a health outcome not identified in the remaining literature.

The remaining studies were sorted into dietary intake studies, controlled exposure studies, and studies of acute exposure to OSP for colonoscopy preparation. These studies were then screened to determine whether they met the criteria listed below. Studies meeting the criteria were tabulated and evaluated for their potential to support a quantitative evaluation of dose-response. The studies retained include those that met the following conditions:

- Controlled exposure to Na_3PO_4:
  1) The study must evaluate a noncancer toxicological endpoint associated with oral intake. Studies evaluating whether phosphate supplementation improves athletic performance, those assessing beneficial effects of P supplementation on patients with hypophosphatemia, or those evaluating cotreatment with another agent were not included.

- Monitored dietary phosphate intake:
  1) The study must use cohort or case-control design. Cross-sectional studies of dietary intake and health outcomes were not generally considered sufficiently robust to use in dose-response assessment because intake and effect are assessed at approximately the same time, making them susceptible to recall bias and unable to support a temporal relationship between outcomes and exposure. However, these studies may provide information on potential indicators of hazard. Thus, they are discussed broadly but not included in the studies evaluated for dose-response.
  2) The study must evaluate a noncancer or cancer endpoint associated with the oral exposure route. Studies assessing only biomarkers of exposure, such as serum electrolytes, PTH, fibroblast growth factor-23 (FGF-23), or Klotho protein were excluded. The toxicological significance of changes in the levels of these biomarkers is unclear.

- Acute exposure to a sodium phosphate bowel preparation:
  1) The study must use cohort or randomized prospective design. Case reports and case series were not tabulated. They are discussed qualitatively in the text.
  2) The study must evaluate sensitive noncancer toxicological outcomes, such as serum creatinine. Studies focused on bowel cleansing efficacy that included only patient-reported symptoms (e.g., nausea, vomiting) were not included.
  3) The study must include a comparison group not exposed to sodium phosphate (e.g., studies comparing oral versus enema administration of sodium phosphate were not included). The comparison group may be exposed to another bowel cleansing agent (e.g., polyethylene glycol [PEG]).
  4) Studies describing the occurrence of aphthous (stomatitis) lesions in the intestinal mucosa after sodium phosphate administration are not tabulated, because they did not have information on the condition of the mucosa prior to sodium phosphate exposure. However, these lesions and their potential relationship to sodium phosphate exposure are discussed in the text.

Appendix A provides a flow chart showing the disposition of human studies from the literature searches.

In addition to the European Food Safety Authority (EFSA) literature search results (EFSA, 2015, 2005), recent published reviews assessing the human health effects of elevated dietary P intake (Chang and Anderson, 2017; Brown and Razzaque, 2015; Hong et al., 2015; Nadkarni and Uribarri, 2014; Anderson, 2013; Calvo and Tucker, 2013; Gutiérrez, 2013; Jain and Elsayed, 2013; Menon and Ix, 2013; Uribarri, 2013) were consulted to provide context for the results from the qualified human data and relevant information on associations between health endpoints and serum P or other biomarkers.

Most of the human studies selected for qualitative or quantitative consideration in the assessment of phosphate noncancer effects, including all of the bowel preparation studies, describe associations between exposure and renal effects; these studies are discussed in the following subsection. Later subsections discuss studies of cardiovascular, skeletal/bone, and other (miscellaneous) noncancer effects. Studies of cancer endpoints are discussed under subsections for prostate cancer and other cancers. Each subsection is followed by one or more tables summarizing key elements of the studies that met selection criteria. The tabulated

information includes study design features (population, exposure, and outcome assessment), results (with covariates considered or included), and some strengths and limitations of each study.

Renal Effects in Humans

Tables 4 (dietary intake) and 5 (acute exposure for bowel preparation) show studies of renal effects that met criteria for dose-response consideration.

Controlled Exposure Studies

Limited information on renal effects was obtained from controlled exposure studies. In a controlled exposure study described below in the "Cardiovascular Effects and All-Cause Mortality in Humans" section, Chang et al. (2017) did not observe a statistically significant relationship between P supplementation (2,206 mg P/day during supplementation versus 1,364 mg P/day during control period, including background) for 3 weeks and urinary albumin in a randomized crossover trial of 31 patients with early stage chronic kidney disease (CKD). In another cross-over design study in which urinary levels of microalbumin, α1-microglobulin, and β2-microglobulin were measured after 6 weeks of P supplementation (as sodium phosphate tablets and orange juice fortified with P), the only observed change was a nonsignificant decrease in microalbumin (Grimm et al., 2001) (see "Skeletal/Bone Effects" section and Table 7).

Dietary Intake Studies

Only one dietary intake study met selection criteria for dose-response consideration (see Table 4). No cross-sectional studies examining the association between renal effects and dietary P were found in the literature reviewed. Yoon et al. (2017) evaluated incident CKD among participants aged 40−69 years in the Korean Genome and Epidemiology Study. The study authors assessed glomerular filtration rate (GFR) and proteinuria every 2 years in 873 subjects with diabetes mellitus and 5,846 subjects without diabetes; the mean follow-up time was 8 years. Intake of P was assessed by semiquantitative 1-day recall food frequency questionnaire (FFQ) administered by trained interviewers at baseline and 4 years later. Yoon et al. (2017) did not report the number of items considered in the FFQ. They did indicate that it had been validated as a general nutrient exposure assessment tool. The mean P intake in the participants was 959 mg P/day.

The study authors analyzed the association between incident CKD and P intake in quartiles of P dietary density (g P/total daily calorie intake) in subjects with and without diabetes mellitus. P intakes in the first through fourth quartiles of dietary density were 753, 903, 1,022, and 1,185 mg P/day. No association between P intake and incident CKD was seen in subjects without diabetes. In subjects with diabetes mellitus, the hazard ratio (HR) for CKD exhibited a nonsignificant increase in Quartiles 2 and 3 of dietary P density, when compared with the first quartile, whereas a significantly increased risk of CKD was observed in the highest quartile (HR = 1.68, 95% confidence interval [CI] = 1.08−2.63. The study authors controlled for several covariates in their analysis but did not control for concurrent Ca intake, or for a dietary source of P (organic or inorganic; plant, animal, or additive).

Identification of effect levels from this study was complicated by the fact that the HR for CKD was increased in Quartiles 2–4 for dietary P intakes when compared with Quartile 1. Thus, the P intakes that represent the LOAEL and NOAEL are not immediately clear. Because the HR

was increased statistically significantly in the fourth quartile, an approximate LOAEL of 1,185 mg P/day is identified on the basis of P intake in the fourth quartile. This intake estimate corresponds to an approximate dose of 16.93 mg P/kg-day based on a default human body weight of 70 kg (mean body weight of subjects was not reported). A NOAEL is approximated on the basis of the intake in the third quartile of 1,022 mg P/day, corresponding to 14.6 mg/kg-day.

Serum Phosphorus Studies

Several studies have reported an association between serum or urine P levels and progression of CKD or development of end-stage renal disease [as reviewed by Chang and Anderson (2017); Nadkarni and Uribarri (2014)]. These studies are limited by the use of serum or urine biomarkers to assess exposure to P (due to tightly controlled homeostatic mechanisms), as well as potential for reverse causation. Progression of renal disease impairs excretion of P, leading itself to higher serum P. In addition, there is evidence that, as kidney function declines in patients with CKD, they decrease their protein intake, with consequent decreases in phosphate intake [as reviewed by Chang and Anderson (2017)]; thus, increases in serum P may not reflect increased intake, but rather decreased excretion. There is some support in the literature indicating that restriction of dietary P intake limits the progression of CKD [as reviewed by Nadkarni and Uribarri (2014)]. This finding likely forms the basis for medical recommendations to restrict phosphate intake and the use of phosphate binder therapeutic agents, in patients with CKD.

Studies of Oral Sodium Phosphate Use for Bowel Preparation or Constipation

Beginning in the 1990s, OSP preparations (e.g., Fleet Phospho-Soda) were used for bowel cleansing in preparation for colonoscopy. OSP preparations were often better tolerated by patients than were the other bowel cleansing options at the time (e.g., PEG solution), which required consumption of large volumes (4 L) of fluid. The OSP dosing regimen used typically consisted of two 45 mL solutions, each administered with 8 ounces of water, 10−12 hours apart (the night before and the morning of scoping) (Marshall, 2014; Markowitz and Perazella, 2009). The total 90 mL dose included 43.2 g of NaH_2PO_4 and 16.2 g of Na_2HPO_4, containing a total of 11.6 g of P (Markowitz and Perazella, 2009), which is equivalent to a dose of 164 mg P/kg in 1 day for a 70-kg adult. Contraindications against use of OSP preparations included advanced age, renal insufficiency, and other conditions that could influence fluid and electrolyte balance (Marshall, 2014).

Case reports and case series describing acute kidney injury (acute phosphate nephropathy) after use of OSP preparations for bowel cleansing began to be published as their use became more common (Connor et al., 2008; Ori et al., 2008; Slee et al., 2008; Beyea et al., 2007; Ma et al., 2007; Markowitz et al., 2005; Markowitz et al., 2004; Orias et al., 1999). In December 2008, after receiving several adverse event reports, the FDA required a “black box” warning to be included on Fleet Phospho-Soda over-the-counter products and warned that it should no longer be used for colonoscopy preparation (Marshall, 2014; Markowitz and Perazella, 2009). The bases for the FDA action included the case reports of acute kidney injury and evidence from biopsies (calcium phosphate deposits) that supported a causal relationship.

In a meta-analysis that reported a nonsignificant pooled odds ratio (OR) for kidney injury, Brunelli et al. (2009) suggested that instances of acute kidney injury resulted from OSP use in persons with pre-existing kidney disease (a contraindicated use) or in individuals who did not follow hydration recommendations during use. Although compliance with contraindications

and recommended hydration is important in assessing safety of OSP for medical purposes, these concerns do not apply to assessment of hazard to humans exposed to sodium phosphates in the environment.

A number of epidemiological studies published after the 2008 FDA action (Lee et al., 2017; Layton et al., 2014; Kan et al., 2012; Seol et al., 2010) (see Table 5) reported no increased risk of acute kidney injury with OSP use. However, as Table 5 shows, the study populations evaluated in these investigations excluded susceptible populations (those with inadequate renal function or other contraindications to use), which may explain the lack of toxicological outcomes in the studies published after the FDA restrictions were enacted.

Sodium phosphate preparations (both oral and enema versions) were also available over the counter for use to relieve constipation. A typical oral product contained 21.6 g NaH_2PO_4 and 8.1 g of Na_2HPO_4, P in one adult dose (3 tablespoons in 24 hours), containing a total of 7.34 g of P (equivalent to a dose of 105 mg P/kg-day for an adult weighing 70 kg). For children aged 5−9 years, the recommended dose was 0.5 tablespoons in 24 hours, equivalent to 1.22 g P or approximately 40 mg P/kg-day for a 30 kg child. In 2014, FDA published an additional warning pertaining to the use of oral and rectal sodium phosphate preparations for constipation relief. FDA (2014) warned that exceeding the recommended dose (40−105 mg P/kg-day in people ≥5 years of age) or use of these products in children under 5 years of age (except under physician direction) can lead to renal or cardiovascular injury or death via dehydration and electrolyte imbalances. The warning noted the following particularly susceptible populations: young children; individuals older than 55 years; patients who are dehydrated; patients with kidney disease, bowel obstruction, or inflammation of the bowel; and patients who are using medications that may affect kidney function (diuretics or water pills; blood pressure medications including angiotensin converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]; and nonsteroidal anti-inflammatory drugs such as aspirin, ibuprofen, and naproxen).

Table 4. Selected Cohort Studies Evaluating Associations between Phosphorus Intake and Renal Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Yoon et al. (2017) (Korea): 873 subjects with DM and 5,846 without (non-DM); participants in Korean Genome and Epidemiology Study; recruited from June 2001 on; aged 40−69 yr. There were 454 males (52%) and 419 females. Body weights were not reported. The mean age was 55.6 yr. Health status reported 28.8% hypertension, 4.4% cardiovascular disease, 16.2% gastritis/ulcer, and 1.5% malignancies. Other health outcomes were not reported.	Intake assessed using validated semiquantitative 1-d dietary recall FFQ (number of items not reported) administered by trained interviewers, once at baseline and again 4 yr later. P content estimates were obtained from 2011 nutrient database of Korean Nutrition Society. Mean intake: 959 mg P/d.	Incident CKD was defined as a composite of estimated glomerular filtration rate <60 mL/min/1.73 m^2 or the development of proteinuria, evaluated biennially from 2001 to 2014.	P density in the highest quartile (in which the mean intake was 1,185 mg P/d was associated with an increased risk of CKD (compared with lowest quartile) in DM subjects; HR = 1.68 (1.08−2.63). No association was seen in non-DM subjects. Covariates in final model: Age, sex, waist-to-hip ratio, average protein intake, education, income, marital status, smoking status, history of hypertension, fasting glucose, serum albumin, and HDL cholesterol.	Strengths: Relatively long follow-up (mean 8 yr). Limitations: Short-term food frequency estimates; highest quartile of intake was less than typical U.S. intake; does not distinguish between organic and inorganic P sources; did not control for Ca intake.

Ca = calcium; CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FFQ = food frequency questionnaire; HDL = high-density lipoprotein; HR = hazard ratio; P = phosphorus.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Abaskharoun et al. (2007) (Canada): Retrospective cohort study of 767 patients (324 females/443 males) given either an OSP (*n* = 618) or PEG (*n* = 149) purgative prior to colonoscopy, who had available serum CR levels. No eligibility restriction for baseline kidney function. Body weight was not reported. Mean age was 55.1 yr. 9.8% had diabetes, 11.1% had cardiovascular disease, 3.4% had peripheral vascular disease, 1.8% had kidney stones, 0.3% had CKD, and 26.2% had hypertension. Other health outcomes were not reported.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Renal function assessed by serum CR and estimated CR clearance immediately before colonoscopy and again 3 mo to 9 yr later (mean 3.7 yr in OSP group and 1.0 yr in PEG group) at repeat colonoscopy.	No significant difference was observed between the two groups in the proportion of patients developing renal insufficiency (serum CR greater than the upper limit of normal) or in the change in CR clearance. Further, multivariate analysis did not show type of purgative as an independent predictor of renal insufficiency. Covariates in multivariate analysis: Age, sex, comorbid conditions, and medications.	Strengths: Moderately large sample size. Limitations: Study funded by OSP manufacturer. Comparison group exposed to PEG; more women in OSP group, and more patients with chronic disease and taking medications in PEG group; time to repeat CR measurement differed significantly between groups, and included some as long as 9 yr after exposure; laboratory changed upper limit of normal CR level between 80 and 100 µmol/L.
Brunelli et al. (2007) (United States): Nested case-control study of 116 cases of kidney injury (93 females/39 males) and 349 control colonoscopy patients (227 females/171 males) who did not meet criteria as cases, with data on the purgative used prior to the procedure. Mean ages were 65 yr (cases) and 63 yr (controls). Eligibility was restricted to those with baseline serum CR ≤1.5 mg/dL. Body weights were not reported. Diabetes was noted in 38.4%, congestive heart failure was noted in 14.6%. Other health outcomes were not reported.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Kidney injury (defined as rise in serum CR of ≥0.5 mg/dL or 25% between values obtained up to 6 mo before and up to 6 mo after colonoscopy).	The odds of using OSP were not higher among cases than by controls (adjusted OR = 0.70, 95% CI = 0.44−1.11). Covariates in multivariate analysis: Age, race, sex, site, diabetes, congestive heart failure, ACEI/ARB, diuretics, and indication (screening or diagnostic colonoscopy).	Strengths: Control for important covariates. Limitations: Small population size. Some controls exposed to other purgatives; more cases than controls were female, had congestive heart failure, and had been exposed to diuretics.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Hurst et al. (2007) (United States): Retrospective cohort study of 9,799 patients given OSP or PEG purgative prior to endoscopy, who had available serum CR levels within 1 yr of the procedure. Eligibility restricted to subjects receiving screening colonoscopy, age ≥50 yr, and without end stage renal disease. No additional eligibility restriction for baseline kidney function. Mean age was 62.9 yr. 54.1% were male. Body weight was not reported. Diabetes was noted in 24.1%, hypertension in 64.0%, cardiovascular disease in 14.0%, congestive heart failure in 3.5%, and CKD in 9.6%. Other health outcomes were not reported.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Acute kidney injury defined as increase of ≥50% in baseline serum CR (values before and after procedure and nearest in date to the procedure were used).	Use of an OSP purgative was associated with increased odds of acute kidney injury (OR = 2.35, 95% CI = 1.51−3.66) compared with use of PEG purgative. Covariates in final model: Age, diabetes, hypertension, atherosclerotic cardiovascular disease, ACEI or ARB use, diuretic use, and factors suspected to be associated with acute kidney injury (e.g., NSAID use, congestive heart failure, CKD, proteinuria, intravenous contrast agent exposure).	Strengths: Large sample size; includes sensitive subpopulations (patients with chronic kidney disease); reliable dose estimate; control for important covariates; study performed prior to FDA (2008) warning on OSPs. Limitations: Comparison group exposed to PEG; differences in comorbidities in the two groups.
Kan et al. (2012) (Taiwan): Retrospective cohort study of 2,270 healthy patients (1,107 females/1,663 males) given either an OSP or PEG purgative prior to colonoscopy, who had available electrolyte levels. No patient with known conflicts and with contraindications was included. Mean age was not reported. Body weight was not reported. Health conditions were not reported.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Renal function indicators (serum CR, eGFR, serum uric acid, urine specific gravity, urine protein) and serum electrolyte levels (Ca, P, sodium, potassium); timing of blood and urine collection was not reported.	Use of an OSP purgative was associated with significantly ($p \leq 0.001$) higher prevalence of hyperuricemia (>9 mg/dL), hypocalcemia (<8.8 mg%), hypernatremia (145−152 mEq/L), hyperphosphatemia (>4.7 mg%), and high Ca × P product (>55 mg^2/dL^2). In multivariate analysis, use of an OSP purgative was associated with increased odds of hyperphosphatemia (OR = 9.49, 95% CI = 7.12−12.72). Male sex reduced the odds of hyperphosphatemia. Covariates in final model: Laxative, sex, age, and BMI.	Strengths: Large sample size; reliable dose estimate. Limitations: Comparison group exposed to PEG; healthy population; limited control for covariates.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Khurana et al. (2008) (United States): Retrospective cohort study of 286 patients (103 males/183 females) with normal serum CR (≤1.5 mg/dL) given OSP purgative for colonoscopy or flexible sigmoidoscopy, compared with control group of 125 patients with similar baseline comorbidities (hypertension, diabetes, use of ACEI, ARB, or diuretics). Mean ages were 68 and 69 yr in OSP and control groups, respectively. Eligibility restricted to those with baseline serum CR ≤1.5 mg/dL. Body weights were not reported. Diabetes was identified in 45% of cases and 50% of controls. Hypertension was identified in 95% of cases and 94% of controls. Other health conditions were not reported.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.52 g P. Intake = 11,520 mg P in 1 d.	Renal function (serum CR and GFR) at 6 mo and 1 yr after enrollment.	Use of an OSP purgative was associated with significantly higher serum CR and lower GFR at 6 mo and 1 yr. Multivariate linear regression analysis showed significant ($p \leq 0.008$) associations between OSP use and: (1) increase in CR level and (2) decrease in GFR (from baseline to 6 mo). Covariates in final models: Age, sex, race, ACEI or ARB use, diuretic use, diabetes mellitus, and hypertension (for analysis of CR); and ACEI or ARB use, diuretic use, diabetes mellitus, and hypertension (for analysis of GFR).	Strengths: Includes some sensitive subpopulations; unexposed comparison group; reliable dose estimate; long-term follow-up. Limitations: More women in control than in OSP group.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Layton et al. (2014) (United States): Retrospective cohort study of patients given either OSP (*n* = 121,266) or PEG (*n* = 429,430) within 1 mo of a screening colonoscopy; age 50−75 yr. Population sampled before FDA warning on OSPs. Analysis also performed on 1:1 propensity-matched (matched on predicted probability of initiating OSP or PEG) subcohorts of 121,203 patients (each, OSP and PEG). Subjects who had used either medication in the prior year were excluded, as were repeat colonoscopies on the same patient. Eligibility was restricted to individuals without acute kidney injury, end-stage renal disease, unspecified renal failure, rhabdomyolysis, dialysis, or renal transplantation in the baseline year. Age of patients was not reported, except a statement that the PEG group was slightly older. Weight of patients was not reported. Sex was not reported, except a statement that there was a slight preponderance of females in the PEG group. Health status was not reported other than a statement that the PEG group had higher prevalence of diabetes, CKD, hypertension, and cardiovascular disease.	Exposure estimated from pharmacy dispensing claims during 30 d before colonoscopy. Standard protocol was two doses of 45 mL each, yielding total dose of 11.52 g P. Intake = 11,520 mg P in 1 d.	Inpatient or outpatient diagnosis of acute renal failure in the 6 mo following colonoscopy that resulted in insurance claim recorded in Truven MarketScan, a U.S. administrative claims database. Mean follow-up time was 170.7 d.	Use of OSP was not associated with increased risk of acute renal failure (compared with PEG) before or after adjustment for potential confounders (adjusted HR = 0.86, 95% CI = 0.75−0.99). There was also no association in subgroups with increased risk of acute renal failure or in analyses using the propensity-matched subcohorts. Covariates considered in analysis (final covariates were not reported; assessed by administrative claims in the baseline year): Diagnoses of kidney stones, hypercalciuria, diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, heart failure, liver disease, kidney disease, atrial fibrillation, systemic lupus erythematosus, or metabolic disorders.	Strengths: Large population; sampling time was prior to FDA (2008) warning on OSPs. Limitations: Comparison group exposed to PEG; administrative claims for baseline and impaired renal function may be insensitive measures; pharmacy dispensing claims are indirect estimates of exposure and do not account for over-the-counter OSP use.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Lee et al. (2017) (Korea): Retrospective cohort study of patients given OSP (n = 109, 57 males/52 females) PEG with ascorbic acid (n = 163, 101 males/ 62 females) or sodium picosulfate ($C_{18}H_{13}Nna_2O_8S_2$) magnesium citrate (n = 93, 56M/37F) purgative for colonoscopy. Eligibility restricted to patients with eGFR ≥60 mL/min/1.73m^2. Body weight was not reported. Mean ages were 47.6 yr in the OSP group, 49.6 yr in the PEG ascorbic acid group, and 50.7 yr in the sodium picosulfate magnesium citrate group. Diabetes was identified in 9.2% of the PEG ascorbate group, 8.6% of the sodium picosulfate magnesium citrate group, and 1.8% of the OSP group. Hypertension was identified in 27, 25.8, and 16.5% in the same groups, respectively.	32 OSP tablets taken in two doses 10 h apart.	Renal function (serum CR and eGFR) and serum electrolytes (sodium, chlorine, P, and Ca) evaluated just prior to colonoscopy and compared with baseline established within 1 mo before.	Use of OSP was not associated with significant difference in eGFR or serum CR. The group given OSP had significantly (p < 0.001) higher serum P and significantly lower serum Ca than both of the other treatment groups. Covariates considered in analysis: Age, sex, smoking, alcohol, diabetes mellitus, hypertension, and BMI.	Strengths: Control for important covariates. Limitations: Small sample size; comparison groups exposed to PEG or sodium picosulfate magnesium citrate; brief follow-up; primary outcome was bowel cleansing efficacy.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Russmann et al. (2007) (United States): Retrospective cohort study of patients of a specific health maintenance organization, given either OSP (*n* = 2,083, 1,158 males/925 females) or PEG (*n* = 269, 137 males/132 females) prior to colonoscopy, who had serum CR measures within the 12 mo before and 6 mo after colonoscopy. Patients with preexisting renal disease (during prior 12 mo) were excluded (eligible patients had eGFR ≥60 mL/min/1.73m^2). Mean age was not reported. Mean weight was not reported. Hypertension was identified in 61.3% of the OSP group and 66.5% of the PEG group. Diabetes was identified in 24.2% of the OSP group and 25.3% of the PEG group. Congestive heart failure was identified in 3.6% of the OSP group and 14.9% of the PEG group. Liver cirrhosis was identified in 1.6% of the OSP group and 3.0% of the PEG group.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.52 g P. Intake = 11,520 mg P in 1 d.	Incident renal impairment (GFR <60 mL/min and change in GFR of >10 mL/min or ≥twofold increase in serum CR between measurements before and after colonoscopy). Cases reviewed by blinded investigators for other causes of renal dysfunction and excluded if another cause was likely.	Use of OSP was not associated with increased risk of incident renal impairment in the 6 months following colonoscopy (adjusted RR = 1.07, 95% CI = 0.51−2.23), even when propensity scoring methodology was used to control for potential confounding. Covariates in final model: Age, sex, African American race, hospitalization within 12 months prior to colonoscopy, hypertension, baseline GFR ≥60 and <90 mL/min, and current use of ACEI, ARB, thiazide, or loop diuretics.	Strengths: Large population size. Limitations: Study funded by OSP manufacturer. Size of comparison group was small. Comparison group exposed to PEG. Serum CR was not determined soon after colonoscopy for all patients, so transient changes in GFR were not captured.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Seol et al. (2010) (South Korea): Retrospective cohort study of patients given OSP (*n* = 224, (149 males/75 females) mean age 47 yr) or PEG (*n* = 113, (81 males/32 females) mean age 51 yr) for screening colonoscopy, compared with control group of 672 (475 males/197 females) age-matched patients (mean age 47 yr) who did not undergo colonoscopy. Eligibility restricted to those with baseline serum CR ≤1.5 mg/dL. Body weights were not reported. Hypertension was identified in 22% of the OSP group, 30% of the PEG group and 28% of controls. Diabetes was identified in 13% (OSP), 20% (PEG), and 20% in controls.	Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Renal function (serum CR and GFR at baseline health evaluation without colonoscopy and at follow-up evaluation without colonoscopy 12−24 mo later). Mean follow-up time was not reported.	Use of OSP was not associated with significant difference in baseline or follow-up serum CR or GFR, or in change in CR or GFR from baseline to follow-up. Covariates in final model: Baseline CR, group, age, sex, medication for hypertension, medication for diabetes mellitus, BMI, and baseline phosphate level.	Strengths: Long follow-up. Limitations: Small exposed population size.

Table 5. Studies Evaluating Associations between Acute Oral Sodium Phosphate (OSP) Intake for Bowel Preparation and Renal Endpoints

Citation (location); Size and Description of Population	P Intake	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations
Singal et al. (2008) (United States): Retrospective cohort study of 311 patients (>96% men) given either OSP (n = 157, (151 males/6 females) mean age 66 yr) or PEG (n = 154, (153 males/1 females) mean age 69 yr) for colonoscopy. Patients without pre- and postprocedure serum CR levels, or with levels >1.5 mg/dL before procedure were excluded. Body weights were not reported. Hypertension was identified in 68.2% of the PEG group and 55.4% of the OSP group. Diabetes was identified in 27.9% in the PEG group and 28% in the OSP group. Coronary artery disease was identified in 29.9 and 22.3%, respectively.	Exposure was determined from chart review. Standard protocol was two doses of 45 mL each, yielding total dose of 11.5 g P. Intake = 11,500 mg P in 1 d.	Renal function (serum CR within 12 mo after colonoscopy, obtained by chart review).	OSP use was associated with slight increase in serum CR that was significantly different from the change induced by PEG (0.04 mg/dL vs. −0.05 mg/dL for PEG; p = 0.005). Likewise, OSP use resulted in an increase in percentage change in serum CR that differed from that induced by PEG (5 vs. −3% for PEG; p = 0.01). In forward logistic regression analysis, OSP use was significantly associated with a ≥25% increase in serum CR (p = 0.003). Covariates in final model: NSAID use and baseline CR.	Limitations: Small population size, very few women (more sensitive sex); few covariates considered.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; CR = creatinine; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; GFR = glomerular filtration rate; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; OSP = oral sodium phosphate; P = phosphorus; PEG = polyethylene glycol; RR = relative risk.

Cardiovascular Effects and All-Cause Mortality in Humans

Table 6 shows three dietary cohort studies and three controlled exposure studies that evaluated cardiovascular effects and all-cause mortality (dietary cohorts only) and met criteria for dose-response consideration. The controlled exposure studies examined effects of phosphate additives or supplements on blood pressure, heart rate, and endothelial function.

Controlled Exposure Studies

Two controlled exposure studies provided direct evidence for an effect of acute increased phosphate intake on endothelial function. Shuto et al. (2009) and Nishi et al. (2015) measured flow-mediated dilation (FMD), a measure of endothelial function, and blood pressure in healthy male volunteers, before and after meals containing additional P in the form of neutralized P supplement. Both studies used a double-blinded crossover design. In both experiments, significant decreases in percent FMD were observed 1−4 hours after the meals; FMD had returned to normal 20−24 hours after the meals. Blood pressure was not affected in either experiment. Nishi et al. (2015) observed that serum P levels were significantly increased at the same time points when percent FMD was significantly decreased. While these studies used small numbers of subjects, the endpoint (FMD) is sensitive, and is predictive of chronic outcomes, as FMD has been shown to correlate with the severity and extent of coronary atherosclerosis (Raitakari and Celermajer, 2000). Acute LOAELs from Shuto et al. (2009) and Nishi et al. (2015) were 19.87 and 26.49 mg P/kg-day, respectively, including dietary intake.

Chang et al. (2017) observed no change in blood pressure in 31 patients with early CKD who were exposed for 3 weeks to food or beverages with or without phosphate additives (998 mg P/day) in a randomized, double-blind crossover trial. In a study evaluating the use of sodium phosphate tablets for chronic constipation (see "Other Noncancer Effects in Humans" section below), 43 patients with irritable bowel syndrome received 2−6 or 4−12 tablets (total doses of 1,770 or 3,541 mg P/day, respectively, excluding dietary contributions) for 28 consecutive days (Medoff et al., 2004). In addition to target endpoints, the investigators measured heart rate and blood pressure for comparison with pretreatment levels. No significant difference in either parameter was observed.

Dietary Intake Cohort Studies

Dietary intake of P was not associated with hypertension in a prospective cohort study of 13,444 subjects from two U.S. cohorts (Alonso et al., 2010). The investigators evaluated the risk of incident hypertension with higher dietary P intake during 11 years of follow-up. Participants were members of the Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) cohorts and were 45−64 and 45−84 years of age, respectively. Dietary intake of P was assessed at baseline using validated FFQs. Systolic and diastolic blood pressure were measured at baseline, and a cross-sectional analysis of the relationship of baseline blood pressure with dietary intake was performed. The subjects were then followed for 11 years, and cases of incident hypertension were identified by measured blood pressure or current use of hypertensive medication. At baseline, higher dietary P was associated with lower blood pressure in cross-sectional analyses. In the prospective study, the risk of incident hypertension decreased with increasing intake of P from dairy sources but not from other sources.

A large (n = 9,686) prospective cohort study of healthy adults recruited from the third National Health and Nutrition Examination Survey (NHANES III) (Chang et al., 2014) did not observe a statistically significant increase in cardiovascular mortality associated with dietary intake of P; however, increased density of P in the diet was significantly associated with increased cardiovascular mortality at densities >0.35 mg P/kcal diet (adjusted HR = 3.39; 95% CI = 1.43−8.02 per 0.1-unit increase in P density in units of mg P/kcal diet [data not shown]). In addition, dietary P intake >1,400 mg P/day was associated with a significant increase in all-cause mortality after adjustment for a range of covariates (adjusted HR = 2.23; 95% CI = 1.09−4.55 per 1-unit increase in natural-log transformed P intake in mg P/day). Consideration of serum P level as a covariate had little to no effect on the magnitude of the association or its confidence limits. Noori et al. (2010a) also reported an increased risk of all-cause mortality (adjusted HR = 2.37; 95% CI = 1.01−6.32) associated with higher dietary P intake in 224 hemodialysis patients; however, interpretation of this finding is complicated by the fact that P homeostasis is impaired in hemodialysis patients, and because 69% of the patients in the study were taking phosphate binders to inhibit absorption of dietary P.

Dietary Intake Cross-Sectional Studies

Cross-sectional studies in which dietary intake of P was measured evaluated associations with blood pressure, coronary artery calcification, coronary artery intima media thickness (IMT), a risk factor for cardiovascular disease, left ventricular hypertrophy, and all-cause mortality. No significant associations between dietary P and blood pressure were observed (after adjustment for covariates) in a study of 4,680 men and women in four different countries (data not shown) (Elliott et al., 2008).

Coronary artery calcification scores were not associated with dietary P intake in a cross-sectional study of 25,652 Korean subjects (data not shown) (Kwak et al., 2014). In a study of 546 healthy male and female subjects in Finland, Itkonen et al. (2013) reported no significant association between total dietary intake of P or P intake from food additives and carotid artery IMT when assessed by quintiles of intake. However, there were significant ($p < 0.05$) trends between energy-adjusted total phosphate intake and increased IMT (in all subjects), and between food additive-derived P and increased IMT (Itkonen et al., 2013).

In an analysis of 4,494 participants in the MESA cohort (data not shown), a significant association was observed between dietary P intake and left ventricular mass measured by magnetic resonance imaging (MRI) (Yamamoto et al., 2013). The study authors estimated that, after adjustment for covariates, a 20% increase in dietary phosphate intake was associated with an increase in left ventricular mass (LVM) of 1.06 g (95% CI = 0.50−1.62 g, $p < 0.001$). Yamamoto et al. (2013) also evaluated risk of left ventricular hypertrophy (LVH) with dietary phosphate intake. LVH, a risk factor for heart attack and stroke, was defined in the study as LVM indexed to body surface area (>85.3 g/m^2 for women or 107.8 g/m^2 for men). The study authors observed higher adjusted odds of LVH among female participants (adjusted Ors ~1.5−3 across quintiles of intake, statistically significant in Quintiles 4 and 5, on the basis of data shown graphically), but not male participants (data not shown) (Yamamoto et al., 2013). Murtaugh et al. (2012) did not observe a statistically significant association between dietary P intake and all-cause mortality in 1,105 subjects with moderate (nondialysis) CKD in a cross-sectional study of NHANES participants (data not shown).

Serum Phosphorus Studies

Much of the epidemiological literature on cardiovascular effects of P consists of studies measuring associations with serum P. Recent reviews of these relationships and their potential mechanisms (Brown and Razzaque, 2015; Gross et al., 2014; Anderson, 2013; Gutiérrez, 2013; Jain and Elsayed, 2013) point to increased risks of vascular calcification and atherosclerosis, LVH, general cardiovascular disease, and mortality from cardiovascular disease with increases in serum P. Vascular calcification reflects the deposition of calcium phosphate (usually as apatite) in the cardiovascular system (blood vessels, valves, and myocardium) [as reviewed by Gross et al. (2014)]. Several studies, including large prospective cohort studies, have demonstrated associations between higher serum P and increased Ca in the coronary arteries in people with moderate and advanced CKD, but also in healthy adults [as reviewed by Gross et al. (2014)]. Although dietary P intake was not a predictor of coronary artery calcification scores in the cross-sectional study reported by Kwak et al. (2014) (discussed under dietary intake), serum Ca, serum P, and Ca × P product were significantly associated with increased calcification scores in the three highest quartiles (compared with the lowest quartile). Other studies have also shown that elevated serum P is associated with increased arterial stiffness and carotid vessel disease [as reviewed by Gutiérrez (2013)] and an increased risk of LVH or increased LVM [as reviewed by Brown and Razzaque (2015); Gutiérrez (2013)]. Additional support for the relationship between serum P and cardiovascular disease comes from studies showing higher frequencies of cardiovascular events or higher mortality from cardiovascular disease with higher levels of serum P (Brown and Razzaque, 2015; Anderson, 2013; Jain and Elsayed, 2013). In contrast, when urinary P excretion or the ratio of P to creatinine in urine was used as a biomarker for phosphate homeostasis, no association with cardiovascular disease mortality was observed (Dominguez et al., 2013 as cited in Gutiérrez, 2013).

The serum studies, supported by mechanistic evidence for effects of circulating P on cardiovascular health, provide a relatively robust link between cardiovascular effects of increased serum P. However, as there is a tenuous link between serum P and intake of P, studies using serum P as a biomarker of exposure are less robust. Thus, these data are of limited utility for assessment of inorganic phosphate toxicity, and specifically for Na/K salts.

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Dietary cohort studies				
Alonso et al. (2010) (United States): 13,444 participants in two population-based cohorts: ARIC (*n* = 9,785 for cross-sectional analysis and *n* = 8,208 for longitudinal analysis) and MESA (*n* = 3,659 for cross-sectional analysis and *n* = 2,901 for longitudinal analysis); age at baseline 45−64 yr (ARIC) and 45−84 yr (MESA). Sex distribution was not reported. Age and weight reported by phosphorus intake quintile. Age averages were 52.8, 53.4, 53.5, 53.9, and 53.7 yr. Average body weights were 75.2, 76.0, 75.7, 76.5, and 76.8 kg.	Intake was assessed by validated FFQ (66 items for ARIC and 120 items for MESA); nutrient content source was not specified for ARIC; source for MESA was the Nutrition Data Systems for Research Database.	Systolic and diastolic blood pressure at baseline; incident hypertension, based on blood pressure measurement (at follow up visits every 2−3 yr) or current use of antihypertensive medication. Follow-up was 11 yr (ARIC) or 7 yr (MESA).	In cross-sectional analyses, higher dietary P intake was associated with decreased baseline systolic and diastolic blood pressures in both cohorts and in pooled analysis. In longitudinal analysis, the HR for incident hypertension decreased across quintiles of P intake from dairy products, but the relationship did not hold for P intake from nondairy sources. Covariates in final model: Age, race, sex, BMI, waist circumference, eGFR, education, income, physical activity, cigarette smoking, study site, alcohol intake, and energy intake.	Strengths: Longitudinal design; large and diverse populations; validated exposure assessment method; clearly defined outcome assessment; consideration of known confounders; consideration of P source. Limitations: Diet assessed only at baseline.

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Chang et al. (2014) (United States): 9,686 nonpregnant healthy adults without diabetes, cancer, or kidney or cardiovascular disease, recruited from NHANES III, 1988−1994; aged 20−80 yr at baseline. Sex distribution was not reported. Age and health status (hypertension only) were reported by phosphorus intake quartiles. Average body weights were not reported. Age averages were 42.5, 42.6, 41.0, and 38.5 yr. Hypertension incidence was 19.6, 17.6, 16.0, and 15.8%.	Intake was assessed by FFQ (24-h dietary recall, recorded by trained interviewers); content estimates were obtained from USDA Survey Nutrient Database. Exposure was assessed both as absolute P intake and P density. Median intake = 1,166 mg P/d.	All-cause and cardiovascular mortality abstracted from NHANES III mortality file through December 31, 2006; cardiovascular mortality definition from ICD, 10th edition.	P intake >1,400 mg P/day was associated with increased all-cause mortality (adjusted HR = 2.23; 95% CI = 1.09−4.55 per 1-unit increase in natural-log-transformed P intake in mg P/d). The association remained when serum P was added as a covariate, and a similar association was seen for P density >0.35 mg P/kcal. P intake (mg P/kg-d) was not associated with increased cardiovascular mortality, while P density (mg P/kg food) was. Covariates in final model: Age, sex, race, ethnicity, poverty:income ratio, total energy intake, BMI, systolic blood pressure, current and former smoking, physical activity, non-HDL cholesterol, log albumin:creatinine ratio, eGFR, and low vitamin D concentration.	Strengths: Longitudinal design; large population size; clearly defined outcome assessment; consideration of known confounders. Limitations: Diet assessed by 24-h recall; no consideration of P source (e.g., organic or inorganic).

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Controlled exposure studies				
Chang et al. (2017) (United States): 31 adults (21 males and 10 females) with early CKD (eGFR ≥45 mL/min/1.73 m^2 and urine albumin:creatinine ratio ≥17 mg/g in men or 25 mg/g in women); randomized double-blind crossover trial. Body weights were not reported. In the two groups (low to high and high to low), the mean ages were 64.2 and 68.0 yr. Females were 25% in the first group and 40% of the second. Hypertension was identified in 81 and 93% respectively. Diabetes was identified in 50 and 47%. Dyslipidemia was identified in 50 and 67%. Coronary artery disease was identified in 13 and 7%.	After a 2-wk run-in period, participants were given a breakfast bar and 65 ounces of diet beverages with or without phosphate additives (additives provided 998 mg P/d) for 3 wk. After the first period and a 2-wk washout period, subjects crossed over to the other treatment for an additional 3 wk. Ca content of the P foods was higher than that of the foods without P (1,050 vs. 800 mg Ca/d). Total intake: 1,364 mg P/d in additive-free period or 2,206.1 mg P/d in additive period.	Blood pressure was measured, and blood and 24-h urine samples were collected at the end of each period; blood was analyzed for P, intact PTH, and FGF-23; urine was analyzed for albumin, P, and Ca.	Participants reported GI symptoms at approximately the same frequency in both treatment periods. Intake of P additives did not significantly alter urinary albumin or serum P or FGF-23. Blood pressure was not altered by exposure. Intact PTH was significantly increased after the additive exposure period (compared with additive-free period). Urinary excretion of P and Ca was significantly higher during the P additive period compared with the additive-free period. NOAEL = 24.87 mg P/kg-d (including diet) based on reported mean body weight of 88.7 kg during additive period. Alterations in serum intact PTH and urinary P and Ca were not considered to be toxicological.	Strengths: Robust study design; duration of 3 wk. Limitations: Small sample size; background diet changed during treatment; limited endpoints evaluated.

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Nishi et al. (2015) (Japan): 16 healthy male volunteers with a mean age of 23.4 yr; double blinded crossover design. Body weight was not reported.	Participants consumed meals at three different times (1 wk between meals) containing 400, 800, or 1,200 mg P (supplemental P provided as neutralized phosphate supplement); breakfasts and dinners on these days contained 400 mg P/meal. Participants served as their own controls. Total intake: 1,200, 1,600, or 2,000 mg P/d on 1 d.	Blood samples were obtained, and blood pressure and FMD (a measure of endothelial function) were measured immediately before the test meal and 1, 2, 4, and 20 h after the test meal. Serum levels of minerals, intact PTH, glucose, insulin, high, sensitive C-reactive protein, monocyte/macrophage chemoattractant protein-1, and FGF-23 were measured.	Percent FMD was significantly decreased (compared with 400 mg P/d meal) after the 800 and 1,200 mg P/d meals at 1, 2, and 4 h after the test meal, but not 20 h after the meal. The degree of change in percent FMD did not differ between the two dose groups. Serum P levels were significantly increased at the same time points. Systolic and diastolic blood pressure and other serum chemistry endpoints were not affected by the test meal. LOAEL = 26.49 mg P/kg-d (including diet) for transient decrease in percent FMD, based on reported mean body weight of 60.4 kg.	Strengths: Robust study design; Ca intake held constant across exposure groups. Limitations: Small number of subjects; single exposure.

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Noori et al. (2010a) (United States): 224 patients on maintenance hemodialysis, participants in the NIED cohort; mean age 55 yr; 69% of patients were taking P binders. Average body weight was not reported. Age, sex, and health status (diabetes only) were reported by phosphorus intake tertile. The mean ages were 54.0, 57.7, and 54.4 yr. Female sex was 57, 46, and 41%. Diabetes was identified in 57, 64, and 60%, respectively, in the three tertiles.	Intake for prior 6−12 mo was assessed by validated questionnaire (Block Food Frequency Questionnaire; 107 items) administered by trained interviewers; P content estimates obtained from USDA food ingredient data. Intake ranged between ~250 and 2,000 mg P/d.	All-cause mortality; methods not reported.	Highest tertile of P intake was associated with increased risk of death compared with lowest tertile; adjusted HR = 2.37 (95% CI = 1.01−6.32) after adjustment for covariates. The association remained after adjustment for additional confounders including serum cholesterol (data not shown). Covariates in final model: Age, sex, race/ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), intake of P binders, residual urine, energy, protein, and potassium intake, serum concentrations of albumin, creatinine, bicarbonate, ferritin, Ca, and P, blood levels of Hb, WBC, and lymphocyte percent; and normalized protein catabolic rate, nPCR, BMI, and averaged doses of erythropoietin and injected active vitamin D; serum concentrations of c-reactive protein, interleukin-6, and tumor necrosis factor-α.	Strengths: Control for important covariates. Limitations: Small sample size; intakes reported only as tertiles without absolute values; brief follow-up (5 yr); methods for mortality assessment not reported; most participants were taking P binders.

Table 6. Studies Evaluating Associations between Phosphorus Intake and Cardiovascular Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Shuto et al. (2009) (Japan): 11 healthy male volunteers, mean age 24.6 yr; double blinded crossover design. Body weight was not reported.	Participants consumed a single meal containing either 400 or 1,200 mg P (supplemental P provided as neutralized phosphate supplement). Intake at other meals was not reported. Participants served as their own controls. Intake: 400 or 1,200 mg P/d on 1 d (not including diet).	Blood samples were obtained, and blood pressure and FMD were measured immediately before the test meal and 2 h after the test meal. Serum minerals, intact PTH, glucose, cholesterol, and triglycerides were measured.	Percent FMD was significantly decreased, and serum P was significantly increased 2 h after the meal (compared with premeal measures); FMD returned to normal within 24 h. Blood pressure and other serum chemistry measures were not affected by treatment. LOAEL = 19.87 mg P/kg-d (not including diet) for transient decrease in percent FMD, based on reported mean body weight of 60.4 kg.	Strengths: Robust study design. Limitations: Small number of subjects; single exposure; P intake at other meals not reported.

[a]Nutrient databases in general are believed to underestimate P intake [as reviewed by McClure et al. (2017); EFSA (2015)]; this is a limitation of all the dietary cohort studies.

ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FFQ = food frequency questionnaire; FGF-23 = fibroblast growth factor-23; FMD = flow-mediated dilation; GI = gastrointestinal; Hb = hemoglobin; HDL = high-density lipoprotein; HR = hazard ratio; ICD = International Classification of Diseases; LOAEL = lowest-observed-adverse-effect level; MESA = Multi-Ethnic Study of Atherosclerosis; NHANES III = Third National Human and Nutrition Examination Survey; NIED = Nutritional and Inflammatory Evaluation in Dialysis; NOAEL = no-observed-adverse-effect level; nPCR = normalized protein catabolic rate; P = phosphorus; PTH = parathyroid hormone; USDA = U.S. Department of Agriculture; WBC = white blood cell.

Skeletal/Bone Effects in Humans

Table 7 summarizes studies that examined potential associations between dietary intake of phosphate and effects on the skeleton/bone. Five prospective cohort studies met inclusion criteria; of these, one study was of adults and the remaining four were birth cohort studies. The available data suggest a potential association between P intake and *improved* bone health, but several important confounding factors limit the conclusions that can be drawn.

In a cohort study of 46- to 68-year-old men (Elmståhl et al., 1998), the odds of a bone fracture were decreased with increasing dietary P intake during 2.4 years of follow-up.

The first birth cohort study (Bounds et al., 2005) evaluated the association between children's P intake and bone development in a cohort of 52 children. P intake was evaluated by FFQs completed by the children's mothers on eight occasions between the ages of 2.3 and 8 years. In addition to the maternal exposure studies, Bounds et al. (2005) also observed a positive association between P intake and bone mineral content (bmc) at age 8 years, and no association with bone mineral density (bmd). Three additional birth cohort studies (Jones et al., 2000 as cited in EFSA, 2015; Heppe et al., 2013; Yin et al., 2010; Tobias et al., 2005) examined whether maternal intake of P during pregnancy influenced bmd or bmc in children between 8 and 16 years of age. In these studies, maternal intake of P was either positively associated with measures of bmc or bmd.

One controlled exposure study that met inclusion criteria also examined bone endpoints. Grimm et al. (2001) used a cross-over design to evaluate the effects of 6 weeks of P supplementation (as sodium phosphate tablets and orange juice fortified with P) on markers of bone metabolism in young adult women (23−39 years old). The supplementation period was preceded by a 4-week period in which mean P intake was controlled at 1,700 mg P/day. Compared with the control period, supplementation with mean P at 3,008 mg P/day did not induce significant differences in serum minerals or hormones, although serum osteocalcin was significantly lower in the washout period than in the control period. Levels of urinary pyridinoline and deoxypyridinoline were higher during supplementation, but marked interindividual variability was noted, and differences from the control period were not statistically significant.

In general, cross-sectional studies (Lee and Cho, 2015; Lee et al., 2014; Haraikawa et al., 2012; Ito et al., 2011; Nakamura et al., 2004; Méndez et al., 2002; Whiting et al., 2002; Brot et al., 1999) showed that P intake was either not associated with measures of bone health, or a positive association was noted between higher P intake and improved bone health.

Evaluation of the impact of P intake on bone health is confounded by the influence of Ca. Brot et al. (1999) observed positive associations between Ca:P intake ratio and bmc and bmd in peri-menopausal women, implying that a low Ca:P ratio is associated with lower bmc and bmd. Thus, increasing P levels while Ca intake remains unchanged could have negative effects on bone, but the available data are inadequate to support this conclusion. Finally, inorganic phosphate is a significant source of inorganic acid load in the diet [as reviewed by Calvo and Tucker (2013)]. Dietary acid load was associated with bone catabolism in some studies [as reviewed by Calvo and Tucker (2013)], suggesting one possible mechanism by which higher intake of inorganic phosphates could adversely affect bone status.

In summary, available human data do not provide clear evidence for an association between dietary intake of P and toxicological effects on bone health. Interpretation of the available data is confounded by the role of adequate Ca intake, dietary acid load, and varying bioavailabilities of different dietary sources of P.

Table 7. Selected Studies Evaluating Associations between Phosphorus Intake and Bone Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Dietary cohort studies of adults				
Elmståhl et al. (1998) (Sweden): 6,576 randomly selected male residents of Malmö, aged 46−68 yr, recruited between 1991 and 1994 into the Malmö Diet and Cancer cohort. Body weight was not reported. Health conditions were not reported.	Intake for prior year was assessed using validated FFQ and 7-d menu book. Content estimates obtained from the Swedish Food Data Base from the National Food Administration.	Incident fractures occurring between 1991 and 1995 and verified by x-ray were identified from registry in the one local hospital with a radiology and orthopedics department.	Lower P intake (<1,357 mg P/d) was associated with an increased odds of bone fracture (RRs ranged between 0.5 and 0.67 in Quintiles 2−5 compared with quintile 1). Covariates in final model: Age, education, marital status, ethnicity, physical activity at work, history of myocardial infarction, stroke or hypertension (yes/no), smoking, intakes of energy, fat, vitamin D, and Ca, and of zinc and P by quintiles.	Strengths: Food frequency estimate for prior year; control for nutrient covariates potentially related to fractures. Limitations: Brief follow-up period (mean 2.4 yr); no consideration of P source.
Birth cohort studies of dietary intake				
Bounds et al. (2005) (United States): 52 healthy children (25 males and 27 females) and their mothers, participants in 8-yr longitudinal study of children's diet and growth. The mean ages were 8.08 yr for male children, 8.14 yr for female children, and 38.0 yr for the mothers. The mean body weights were 30.5 kg (boys), 27.9 kg (girls), and 69.0 kg (mothers).	FFQ (two food records and one 24-h recall) completed by mothers at nine in-home interviews (when children were ages 2.3, 2.8, 3.5, 4, 4.5, 5, 6, 7, and 8 yr). Mothers were trained in estimating portion sizes and recording intake. Frequencies averaged across 3 d and mean of nine averages was used as longitudinal estimate of intake. Content estimate sources not reported (reported elsewhere). Mean intake across time = 1,063 mg P/d.	Children's bmc and bmd were measured by DXA scan at 8 yr of age.	Children's dietary intake of P was positively associated with bmc ($\beta = 0.11$; $p = 0.01$) but not bmd, at age 8 yr. Covariates considered: Intakes of energy, Ca, vitamin D, P, protein, magnesium, vitamin C, vitamin K, zinc, iron, and caffeine; children's level of sedentary activity; children's sex, height, weight, BMI, and age; and mothers' total bmc or bmd.	Strengths: Longitudinal food frequency estimates. Limitations: Small sample size; did not distinguish between organic and inorganic P sources; serum P not measured.

Table 7. Selected Studies Evaluating Associations between Phosphorus Intake and Bone Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Heppe et al. (2013) (Netherlands): 2,819 mothers and their children (embedded in the Generation R study); mean maternal age at recruitment was 31 yr; children were assessed at median age of 6 yr. Body weights were not reported. The mean ages were 31.6 and 31.5 yr for the Generation R males and females, respectively. Health conditions were not reported.	Maternal intake was assessed using validated semi-quantitative FFQ (293 items) administered at enrollment (median 13.5 wk of gestation) and covering diet patterns over the previous 3 mo; content estimates were obtained from the 2006 Dutch Food-Composition Table. Mean intake = 1,443 mg P/d.	Children's total body bmd, bmc, and bone area were measured by DXA scan at 6 yr of age. Analyses used bmd and bmc for total body minus head.	Increased P intake during pregnancy was associated with higher childhood bmc and bmd (*p*-trend across quintiles <0.001 for both). Quintile intake values were not reported.	Strengths: Food frequency estimate for prior 3 mo. Limitations: Intake quintiles were not reported so it is uncertain whether the intake in the reference group was adequate or deficient. Did not consider children's Ca, P, or other nutrient intake after birth.
Tobias et al. (2005) (England): 4,451 mothers and their children, members of ALSPAC birth cohort; children assessed at mean age of 9−10 yr. The study had two stages. Male mean weights were 33.5 kg at 116 mo in stage 1 and 35.7 kg at 116 mo in stage 2. Female mean weights were 31.4 kg at 116 mo in stage 1 and 36.9 kg at 116 mo in stage 2. Health conditions were not reported.	Maternal intake was assessed using FFQ (75 items) administered at 32-wk gestation; P content estimates were obtained from British food tables. Mean intake = 1,339 mg P/d.	Children's total body and spine-only bmd, bmc, and area-adjusted bmc were measured by DXA scan at ~9 yr of age. Spine data available for 2,466 children. Analyses used bmc for total body minus head and areal bmd.	In univariate analysis, increased P intake during pregnancy was associated with higher total body and spine bmc and bmd, but not area-adjusted bmc. In multivariate models, P intake was not associated with these metrics. Covariates in final model: Age at DXA scan, sex, pubertal stage (girls only), housing, maternal and paternal education, and social class.	Strengths: Control for important covariates. Limitations: Did not consider children's Ca, P, or other nutrient intake after birth.

Table 7. Selected Studies Evaluating Associations between Phosphorus Intake and Bone Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Jones et al. (2000) as cited in EFSA (2015); Yin et al. (2010) (Australia): 216 mothers and their children, participants in birth cohort established in 1988−1989. 70% of the children in the study were male. The average body weight was 67.9 kg. Health conditions were not reported.	Maternal intake during third trimester assessed using one of two self-administered FFQs (151 and 179 items) shortly after birth; P content estimates were obtained from 1991 Australian Tables of Food Composition. Mean intake = 2,314 mg P/d.	Children's femoral neck, lumbar spine, and total body bmd were measured by DXA scan at ages 8 (Jones et al., 2000 as cited in EFSA, 2015) and 16 yr [(Yin et al., 2010)].	Femoral neck and lumbar spine bmd were positively associated with maternal P diet density at age 8 yr; no measure of bmd at age 16 yr was associated with maternal P diet density. Covariates in final model (Yin et al., 2010): Sex, weight at age 16 yr, sunlight exposure in winter at age 16 yr, sports participation, child's current Ca intake, Tanner stage, ever breast-fed, smoking during pregnancy, maternal age at the time of childbirth.	Strengths: Adjusted for child's Ca intake. Limitations: Mean self-reported intake of P much higher than average in Australian pregnant women; did not consider children's P or other nutrient intake after birth.

Table 7. Selected Studies Evaluating Associations between Phosphorus Intake and Bone Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Controlled exposure studies				
Grimm et al. (2001) (Germany): 10 healthy women aged 23−29 yr, (mean 25), mean body weight of 51–69 kg (mean 60 kg), with typical P intakes between 1,060 and 1,810 mg P/d based on 14-d dietary records; crossover design. Health conditions were not reported.	After a 4-wk control period (with mean intakes of 1,700 mg P/d and 1,500 mg Ca/d), participants were given NaH_2PO_4 tablets (containing 620 mg P) and orange juice containing 975 mg P (bringing their total daily intake to 3,008 mg P) for 6 wk; this period was followed by a 4-wk washout period in which intakes were similar to the control period. Ca intake during supplementation was higher (1,995 mg Ca/d) during supplementation than during the control periods (~1,500 mg Ca/d). Total mean intake during supplementation: 3,008 mg P/d.	Symptoms were recorded during supplementation. Blood and urine samples were collected at the end of each period and halfway through the supplementation period. Serum minerals and bone-related hormones were measured, as were urinary levels of pyridinium crosslinks (markers of bone resorption), microalbumin, α1-microglobulin, and β2-microglobulin.	Participants reported diarrhea, soft stools, and intestinal disturbances during supplementation. No significant differences in serum minerals or hormones, although serum osteocalcin was significantly lower in the washout compared with the control period. There was a tendency toward higher levels of urinary pyridinoline and deoxypyridinoline during supplementation, but there was significant interindividual variability. A decrease in urinary microalbumin during treatment was not statistically significant. LOAEL = 50.13 mg P/kg-d (including diet) for GI distress, based on reported mean initial body weight of 60 kg.	Strengths: Duration of 6 wk. Limitations: Small sample size; change in Ca intake during supplementation.

[a]Nutrient databases in general are believed to underestimate P intake [as reviewed by McClure et al. (2017); EFSA (2015)]; this is a limitation of all the dietary cohort studies.

ALSPAC = Avon Longitudinal Study of Parents and Children; bmc = bone mineral content; bmd = bone mineral density; BMI = body mass index; Ca = calcium; DXA = dual-energy x-ray bone densitometry; FFQ = food frequency questionnaire; GI = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; NaH_2PO_4 = monosodium phosphate; P = phosphorus; RR = relative risk.

Other Noncancer Effects in Humans

Early Menarche

In a prospective study examining whether dietary intake of P was associated with premature menarche (defined as menarche before 12 years of age), Ramezani Tehrani et al. (2013) followed 134 prepubertal girls for a median duration of 6.5 years, assessing their pubertal status at clinical interviews every 3 years (Table 8). Dietary intake of P was estimated using FFQs administered at baseline. In this study, higher dietary intake of P (>647 mg P/day) was associated with higher odds of premature menarche (OR = 3.43, 95% CI = 1.45−8.13). This study had several important limitations, especially the very small population size (n = 134), the wide range of ages at entry into the cohort (4−12 years at baseline), and differences in age at baseline between children exhibiting early menarche (mean age 8 years at baseline) and those not exhibiting early menarche (mean age 10 years). Because follow-up examinations took place every 3 years, many of the girls who entered the cohort at mean age 10 years were not followed at all until after the age cutoff for early menarche (12 years). No other studies evaluating onset of menarche and dietary intake of P were identified.

Gastrointestinal Tract

OSP preparations have been used therapeutically to treat constipation and for bowel cleansing prior to colonoscopy; thus, their laxative effects are well established. Additional GI symptoms, including nausea, vomiting, GI distress, and diarrhea (Cheng et al., 2016; Haas et al., 2014; Manukyan et al., 2011; Seo et al., 2011b; Yakut et al., 2010; Patel et al., 2009; Beloosesky et al., 2003; Fine et al., 1998), have been reported in patients using preparations for bowel cleansing. The LOAEL associated with these symptoms after colonoscopy preparation is the same (164 mg P/kg-d) as that identified for risk of acute renal failure under these circumstances (see "Renal Effects in Humans" section above).

For acute OSP use (1−3 days) to treat constipation, a LOAEL of 40 mg P/kg-d can be identified based for laxative effects in children ages 5−9 years (see additional information in the "Renal Effects in Humans" section above). Although laxation is the desired effect in persons voluntarily using sodium phosphate medications, it would be considered to be a toxicological effect in persons unwittingly exposed.

GI symptoms were evaluated in three longer duration controlled exposure studies (Chang et al., 2017; Medoff et al., 2004; Grimm et al., 2001). In a randomized, double-blind crossover trial, GI symptoms occurred at about the same frequency in the treated and untreated periods in 31 patients with early CKD who were treated for 3 weeks with food or beverages with or without phosphate additives (998 mg P/day; see Table 6) (Chang et al., 2017). When 10 healthy female volunteers were given supplemental P (as sodium phosphate tablets containing 620 mg P and orange juice containing 975 mg P) for 6 weeks after a 4-week control period, participants reported higher incidences of GI disturbances during the supplementation period compared with the control period (Grimm et al., 2001) (see Table 7). Finally, in 43 subjects with irritable bowel syndrome presenting primarily as constipation, higher incidences of GI symptoms were reported in the group receiving between 4 and 12 sodium phosphate tablets per day (3,541 mg P/day based on initial target of 8 tablets/day) compared with the group receiving 2−6 tablets/day (1,770 mg P/day based on initial target of 4 tablets/day) (Medoff et al., 2004) (Table 8).

Colonic mucosal abnormalities believed to be attributable to the oral use of sodium phosphate for bowel cleansing have been reported (Coton et al., 2011; also reviewed by Belsey, 2008; Atkinson et al., 2005; Rejchrt et al., 2004; Atkinson and Hunter, 2002; Watts et al., 2002; Driman and Preiksaitis, 1998). These abnormalities are described as shallow aphthous ulcerations or raised nonulcerated rings [as reviewed by Belsey (2008)]. Their cause has not been established. The incidence of such lesions in patients using sodium phosphate for bowel preparation is reported to range between 2.6 and 24.5% (data not shown)[as reviewed by Belsey (2008)]. In one analysis, Rejchrt et al. (2004) observed aphthous lesions potentially associated with sodium phosphate in 21 of 730 colonoscopy patients (data not shown). To rule out inflammatory bowel disease as the cause of the lesions, the study authors followed the patients for 3 years after colonoscopy. None of the affected patients were diagnosed with inflammatory bowel disease during that time (Rejchrt et al. (2004), providing support for attributing the cause of the lesions to sodium phosphate ingestion. Further, the incidence of the lesions was much higher after sodium phosphate use than bowel preparation with PEG in a randomized controlled trial (Zwas et al., 1996 as cited in Belsey, 2008). However, in the absence of colonoscopy or histopathology data from the same patients prior to sodium phosphate use, it is difficult to assign causation. Importantly, Belsey (2008) indicated that these lesions did not have clinical consequences and typically resolved without any medical intervention.

Anemia

In a cross-sectional study, Samuel et al. (2013) observed a significantly higher prevalence of anemia in 366 pregnant women consuming dietary P at the highest tertile of intake (>1,243.3 mg P/day), compared with the lowest tertile (<1,147.1 mg P/day) (data not shown). No additional information pertaining to the potential relationship between anemia and inorganic phosphate intake in humans was identified in the literature reviewed.

Table 8. Selected Studies Evaluating Associations between Phosphorus Intake and Other Endpoints				
Citation (location); Size and Description of Population	**Methods for P Intake Estimation**	**Methods for Outcome Assessment**	**Summary of Results and Covariates Considered**	**Strengths and Limitations[a]**
Dietary cohort studies				
Ramezani Tehrani et al. (2013) (Iran): 134 prepubertal girls; aged 4−12 yr (mean 8.9 yr) at baseline (participants in Tehran Lipid and Glucose Study). Body weights were not reported. Health conditions were not reported.	Children's intake was assessed using two nonconsecutive 24-h dietary recall FFQs administered by dieticians; P content estimates were obtained from nutritionist III software modified for the Iranian food consumption table. Median intake = 647 mg P/d.	Early (defined as <12 yr of age) menarche determined by clinical interview at follow-up examinations every 3 yr (median follow-up 6.5 yr).	Higher P intake (>647 mg P/d) was associated with increased odds of reaching menarche ≤12 yr of age; OR = 3.43 (1.45−8.13). Covariates in final model: Energy and protein intake at baseline, interval between the age at study initiation and the age of menarche, maternal age at menarche, BMI Z-score at baseline, and height Z-score at baseline.	Strengths: Control for important covariates. Limitations: Small population size; age at baseline differed between children with and without early menarche (8 vs. 10 yr, $p = 0.001$); dietary intake assessed only at baseline; short-term intake estimates used; socioeconomic status not considered but known to be related to age at menarche in Iran.

Table 8. Selected Studies Evaluating Associations between Phosphorus Intake and Other Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Controlled exposure studies				
Medoff et al. (2004) (United States): 43 patients with irritable bowel syndrome (IBS), constipation predominant; recruited by researchers who were also gastroenterologists; open-label dose ranging study. Patients were grouped for treatment. Group A was 15 females/3 males with a mean age of 46 yr and a mean body weight of 155 lb. Group B was 20 females/5 males with a mean age of 49 yr and a mean body weight of 162 lb. Health conditions other than IBS were not reported.	Participants were allocated to two groups, receiving either four or eight sodium phosphate tablets (each containing 1.102 g NaH_2PO_4 monohydrate and 0.398 g Na_2HPO_4 anhydrous) for 28 d. The tablets each provided 443 mg P, yielding doses of 1,770 or 3,541 mg P/d when four or eight tablets (respectively) were given. Patients were allowed to increase or decrease the dose depending on symptoms, and in the end, the groups had consumed between 2 and 6 or between 4 and 12 tablets/d. Patients consumed their normal diets during treatment (P and Ca content not reported). Intake: 1,770 or 3,541 mg P/d (not including diet).	Efficacy was assessed by relief of constipation; safety was assessed by monitoring of serious toxicological events, patient-reported symptoms, and measurement of body weight, heart rate, blood pressure, and serum chemistry.	Symptoms reported in the low-dose group included nausea, diarrhea, and incomplete evacuation (1/18 each). In the high-dose group, nausea and diarrhea were reported by 4/25 and 3/25, respectively, and additional symptoms included bloating (2/25) and cramping, headache, lower back pain, migraine, and lower quadrant pain (1/25 each). No effects on body weight, heart rate, or blood pressure. The only serum chemistry change that was considered noteworthy and related to treatment was occasional hypokalemia in five patients (in both dose groups). The study authors concluded that the low dose was well tolerated, suggesting that a starting dose of two to four tablets/day (equivalent to 885−1,770 mg P/d) would be appropriate. LOAEL = 48.2 mg P/kg-d (not including diet) for GI distress and hypokalemia, based on reported mean body weights of 70.3 and 73.5 kg in low- and high-dose groups (respectively).	Strengths: Duration of 4 wk. Limitations: Open label design may confound symptom reporting; actual doses varied from initial targets; dietary P and Ca intake not reported.

[a]Nutrient databases in general are believed to underestimate P intake [as reviewed by McClure et al. (2017); EFSA (2015)]; this is a limitation of all the dietary cohort studies.

BMI = body mass index; Ca = calcium; Na_2HPO_4 = disodium phosphate; FFQ = food frequency questionnaire; GI = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; NaH_2PO_4 = monosodium phosphate; OR = odds ratio; P = phosphorus.

Cancer in Humans

Tables 9 and 10 show dietary cohort and case-control studies (respectively) of cancer that met criteria for dose-response consideration.

Prostate Cancer

The most robust study of prostate cancer risk and dietary phosphate intake was published by Wilson et al. (2015). In this large, prospective cohort study of 47,885 men in the Health Professionals Follow-Up Study, dietary phosphate intake was assessed by FFQ every 4 years during the 24-year follow-up period. Incident prostate cancer was evaluated every 2 years and confirmed by review of medical records and pathology reports. After control for covariates that included known confounders as well as dietary sources of P (dairy and animal protein intake), the risk of incident prostate cancer was significantly increased in the fourth and fifth quintiles of P intake (mean intake 1,783 mg P/day), compared with the first (relative risk [RR] = 1.13, 95% CI = 1.00−1.27), with a significant (p = 0.04) dose-response trend (data not shown). In addition, in analyses stratified by cancer stage, dietary P intake in the highest quintile was associated with elevated risks of lethal cancer (resulting in death or distant metastases; RR = 1.43, 95% CI = 1.02−1.99), advanced-stage cancer (RR = 1.45, 95% CI = 1.08−1.94), and high-grade cancer (based on Gleason scores; RR = 1.51, 95% CI = 1.06−2.17) after adjustment for confounders (data not shown). A significant dose-response trend was seen only for high-grade cancer (p = 0.01).

Three earlier prospective cohort studies of dietary phosphate intake did not observe significant associations with incident prostate cancer (Kesse et al., 2006; Chan et al., 2000) or incident invasive prostate cancer (Tseng et al., 2005). Unlike Wilson et al. (2015), these studies suffered several limitations (see Table 9), most notably the relatively brief follow-up duration. Follow-up averaged approximately 8 years in studies by Kesse et al. (2006) and Tseng et al. (2005), and was between 5 and 8 years in the study by Chan et al. (2000), compared with 24 years in the study by Wilson et al. (2015). In addition, the earlier studies evaluated smaller populations, and did not account for the varying dietary P sources and their bioavailability differences.

In a case-control study (n = 1,294 cases and 1,451 controls) of prostate cancer and dietary P intake (see Table 10), Tavani et al. (2005) did not observe a significant association between the odds of prostate cancer and higher dietary phosphate intake (OR = 1.20, 95% CI = 0.79−1.84), when the highest quintile of intake (>1,897 mg P/day) was compared with the lowest (<1,204.66 mg P/day). Case-control studies can be subject to recall bias if exposure estimates are affected by diagnosis. However, recall bias is less likely in this study because phosphate intake was through an FFQ rather than by direct measurement. It is likely that this study suffers from misclassification of intake because the subjects were asked to remember their diets for the 2-year period prior to disease onset; random misclassification could bias the result toward the null.

No studies examining the association between serum P and prostate cancer were identified in the literature search or published reviews that considered cancer (Brown and Razzaque, 2015; Anderson, 2013; Jain and Elsayed, 2013).

Colorectal Cancer

As shown in Tables 9 and 10, one prospective cohort study Kesse et al. (2005) and one case-control study van Lee et al. (2011) each observed decreased risk of colorectal adenoma or cancer with higher dietary P intake. The adjusted RR for colorectal adenoma in the highest quartile of dietary P intake (>1,633.84 mg P/day) was 0.70 (95% CI = 0.54−0.90) compared with the lowest quartile (<1,141.86 mg P/day) in a cohort of 73,034 women (Kesse et al., 2005). However, the follow-up period was brief (2−7 years), and dietary intake was assessed only once. van Lee et al. (2011) observed a nonsignificant decrease in the adjusted OR for colorectal cancer (OR = 0.78, 95% CI = 0.58−1.05) in the highest quintile of intake (≥1,755.84 mg P/day) compared with lowest quintile (<1,335.29 mg P/day). Trend analysis showed a significant (p = 0.016) trend for decreased OR with increasing P intake. As with the case-control study of prostate cancer discussed above (Tavani et al., 2005), this study is more likely to suffer from random misclassification of exposure than recall bias; in this study (van Lee et al., 2011), cases and controls were asked to fill out FFQs designed to recount diets 10 years earlier.

Bladder Cancer

Another analysis of data from the Health Professionals Follow-Up Study, Michaud et al. (2000) evaluated the risk of incident bladder cancer in 47,909 male cohort members. Dietary intake of P was evaluated by FFQ at baseline (in 1986) and again 4 years later (1990). During 12 years of follow-up, the risk of bladder cancer was not significantly affected (adjusted RR = 0.85, 95% CI = 0.57−1.21) in the highest quintile of P intake (median intake 1,728 mg P/day) compared with the lowest quintile (median intake 1,101 mg P/day). In addition, the test for dose-response trend was not significant (p = 0.40).

Table 9. Selected Cohort Studies Evaluating Associations between Dietary Phosphorus Intake and Cancer Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Prostate cancer				
Wilson et al. (2015) (United States): Prospective cohort study of 47,885 male participants of the HPFS (recruited in 1986; aged 40−75 yr at baseline).	Intake was assessed by semiquantitative FFQ (130 items); administered every 4 yr between 1986 and 2006 and nutrient content of each food. Quintiles with mean intakes of 1,079, 1,248, 1,365, 1,499, and 1,783 mg P/d.	Incident prostate cancer between entry and 2010 (24 yr of follow up); was initially determined by self-report (participant or next of kin) on biennial questionnaire and confirmed by review of medical records and pathology reports. Deaths were determined by questionnaire and National Death Index; cause of death was determined by review of all available data, including death certificate.	Dietary P intake was associated with an increased risk of prostate cancer (all and high-grade subcategory); p for dose-response trend = 0.04; adjusted RR ≥1.11 and significant at $p < 0.05$ in fourth and fifth quintiles compared with first quintile. In addition, in analyses stratified by cancer stage, dietary P intake in the highest quintile was associated with elevated risks of lethal cancer (resulting in death or distant metastases; RR = 1.43, 95% CI = 1.02−1.99), advanced-stage cancer (RR = 1.45, 95% CI = 1.08−1.94), and high-grade cancer (based on Gleason scores; RR = 1.51, 95% CI = 1.06−2.17) after adjustment for confounders (data not shown). A significant dose-response trend was seen only for high-grade cancer (p = 0.01). Covariates in final model: Age in months; calendar time; race; height; BMI at age 21 yr; current BMI; vigorous physical activity; smoking; diabetes; family history of prostate cancer; intakes of tomato sauce, a-linolenic acid, supplemental vitamin E, and alcohol; energy intake; multivitamin use; and history of prostate-specific antigen testing; and Ca, dairy, and animal protein intake.	Strengths: Collection of multiple FFQs over time, high follow-up rates, large sample size, consideration of known confounders, consideration of P source; 24-yr follow-up.

Table 9. Selected Cohort Studies Evaluating Associations between Dietary Phosphorus Intake and Cancer Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Chan et al. (2000) (Finland): Prospective cohort study of 27,062 male participants in ATBC (randomized 2 × 2 trial of alpha-tocopherol and beta-carotene for prevention of lung cancer among smokers); randomly selected from residents of southwestern Finland between 1985 and 1988; median age was between 56.5 and 57.6 yr for quintiles of energy-adjusted Ca intake.	Intake was assessed by FFQ (276 items) administered at baseline and asking about intake over the previous 12 mo; content estimates were obtained from database at National Public Health Institute of Finland.	Incident prostate cancer between 1985 and 1993, initially identified via Finnish Cancer Registry and Register of Causes of Death; diagnosis, and stage verified by review of medical records and histopathology and cytology specimens.	Dietary P intake was not independently associated with prostate cancer risk (adjusted RR = 0.8, 95% CI = 0.4−1.5 comparing highest to lowest quintile of intake: *p* for trend = 0.11). Covariates in final model: Age, smoking, BMI, total energy intake, education, and supplementation group (alpha-tocopherol, beta-carotene, both, or placebo).	Strengths: Large sample size. Limitations: Dietary intake evaluated only at baseline; relatively brief follow-up; did not account for family history.
Kesse et al. (2006) (France): Prospective cohort study of 2,776 male participants in the SU.VI.MAX trial; mean ages of cases and controls were 57.1 and 53.3 yr, respectively.	Intake was assessed by 24-h FFQ (number of items not reported) administered every 2 mo for a total of 5 times in the first 18 mo of the study; content estimates were obtained from 2005 food composition table. Quartiles of energy-adjusted intake were <1,167, 1,167−1,291, 1,291−1,434, and >1,434 mg P/d.	Incident prostate cancer during 7.7 yr (median) of follow-up; determined by self-report at annual follow-up or by death certificate. Cases were verified by independent review of pathology report.	Dietary P intake was not significantly associated with increased prostate cancer risk in any group (adjusted RR comparing highest quartile of intake with lowest quartile = 1.83, 95% CI = 0.89−3.73), although the trend for RR across quartiles was marginally significant (*p* for trend = 0.04). A significant interaction was seen between P and Ca intake (*p* for interaction, *n* = 0.02). Covariates in final model: Occupation, group of treatment, smoking status, overall physical activity level, energy from fat, energy from other sources, alcohol intake, BMI, and family history of prostate cancer in first-degree relative.	Strengths: Collection of multiple FFQs over time, consideration of known confounders. Limitations: Relatively small size and brief follow-up.

Table 9. Selected Cohort Studies Evaluating Associations between Dietary Phosphorus Intake and Cancer Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Tseng et al. (2005) (United States): Prospective cohort study of 3,612 male participants in National Health and Nutrition Examination Epidemiologic Follow-up Study; recruited between 1982 and 1984 during follow-up for longitudinal study begun 1971−1975; mean age at baseline was 57.8 yr.	Intake was assessed by FFQ (105 items) administered at baseline (1982−1984); source for content estimates was not reported. Mean intake was 1,317 mg P/d; median intakes by tertile were: 984.0, 1,218.9, and 1,443.3 mg P/d.	Incident invasive prostate cancer between 1982 and 1984 and 1992 (mean 7.7 yr of follow-up). Cases were determined by: (a) self-report at interviews in 1986, 1987, or 1992; (b) at least one hospital stay with diagnosis coded as invasive prostate cancer; or (c) death certificate with underlying or nonunderlying cause of death coded as invasive prostate cancer.	Dietary P intake was not significantly associated with prostate cancer risk after adjustment for covariates including Ca (*p* for trend = 0.77; adjusted RR comparing highest to lowest tertile of P intake = 0.9, 95% CI = 0.5−1.6). Covariates in full model with Ca: Age, race, energy intake, and design variables; U.S. region; rural, urban, or suburban residence; education; recreational sun exposure; recreational and usual level of physical activity; smoking status; current alcohol intake; and Ca intake.	Strengths: Consideration of many known confounders. Limitations: Dietary intake evaluated only at baseline; relatively small size; relatively brief follow-up; did not account for family history.
Other cancers				
Kesse et al. (2005) (France): Prospective cohort study of 73,034 female participants in the E3N-EPIC cohort established in 1990; mean ages at baseline ranged between 53 and 57 yr. Adenoma study included 516 cases (including 175 with high-risk adenomas) and 4,804 polyp-free noncases; colorectal cancer study included 172 cases and 67,312 noncases.	Intake assessed by validated FFQ (208 items) administered once between 1993 and 1995; content estimates obtained from French national database. Intakes by quartile were: <1,141.86, 1,141.86−1,374.86, 1,374.86−1,633.83, and >1,633.83 mg P/d.	Incident colorectal adenoma between 1993 and 1995 and December 1997, or incident colorectal cancer between 1993−1995 and June 2000 (2−7 yr of follow-up); initially determined by self-report and verified by pathology report.	Dietary P intake was inversely associated with risk of adenoma (*p* for trend = 0.005; adjusted RR comparing highest to lowest quartile = 0.70, 95% CI = 0.54−0.90). Dietary P intake was not associated with risk of high-risk adenoma or colorectal cancer (*p* for trend = 0.23 and 0.11, respectively). Covariates in final model: Education level, current smoking status, family history of colon cancer, BMI, physical activity level and energy, and alcohol intake (at time of dietary questionnaire).	Strengths: Large population size. Limitations: Dietary intake assessed only once; brief (2−7 yr) follow-up; did not account for source of dietary P.

Table 9. Selected Cohort Studies Evaluating Associations between Dietary Phosphorus Intake and Cancer Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Michaud et al. (2000) (United States): Prospective cohort study of 47,909 male participants in HPFS; recruited in 1986; ages 40−75 yr at baseline; men with cancers diagnosed before 1986 were excluded.	Intake was assessed by FFQ (131 items) administered at baseline (1986) and again in 1990; questionnaire asked about dietary patterns over prior year; content estimates obtained from USDA. Median intakes by quintile were: 1,101, 1,250, 1,364, 1,495, and 1,728 mg P/d.	Incident bladder cancer between baseline (1986) and January 31, 1998; initially determined by self-report and confirmed by review of medical records when possible; unreported bladder cancers identified by review of National Death Index were also included.	Dietary P intake was not associated with risk of bladder cancer after adjustment for covariates (*p* for trend = 0.40; adjusted RR comparing highest to lowest quintile of P intake = 0.85, 95% CI = 0.57−1.21). Covariates in final model: Age, pack-years of smoking history, current smoking status, geographic region of the United States, cruciferous vegetable intake, and total fluid intake.	Strengths: Large population size; 12-yr follow-up. Limitations: Dietary intake evaluated only twice.

[a]Nutrient databases in general are believed to underestimate P intake [as reviewed by McClure et al. (2017); EFSA (2015)]; this is a limitation of all the dietary cohort studies.

ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI = body mass index; Ca = calcium; CI = confidence interval; E3N-EPIC = European Prospective Investigation into Cancer and Nutrition; FFQ = food frequency questionnaire; HPFS = Health Professionals Follow-up Study; P = phosphorus; RR = relative risk; SU.VI.MAX = Supplémentation en Vitamines et Minéraux Anti-oxydants; USDA = U.S. Department of Agriculture.

Table 10. Selected Case-Control Studies Evaluating Associations between Dietary Phosphorus Intake and Cancer Endpoints

Citation (location); Size and Description of Population	Methods for P Intake Estimation	Methods for Outcome Assessment	Summary of Results and Covariates Considered	Strengths and Limitations[a]
Tavani et al. (2005) (Italy): 1,294 men with incident prostate cancer and 1,451 controls with nonneoplastic disease or injury; recruited in one of four areas of Italy between 1991 and 2002; mean ages of cases and controls were 66 and 63 yr, respectively.	Intake assessed by FFQ (78 items); content estimates obtained from Italian food composition databases. Quintile upper cut points = 1,204.66, 1,413.51, 1,609.22, 1,897.00, >1,897 mg P/d.	Eligible cases had incident diagnosis of histologically confirmed prostate cancer and were admitted to one of the major teaching and general hospitals in one of the four areas under study. Controls were from the same area and admitted to same network of hospitals with nonneoplastic disease or injury.	P intake was not associated with risk of prostate cancer (adjusted OR = 1.20, 95% CI = 0.79−1.84 for highest quintile compared with lowest; *p* for trend = 0.39). Covariates in final model: Age, center, education, body mass index, tobacco smoking, physical activity, total energy, and family history of prostate cancer.	Strengths: Large size. Limitations: Potential for recall bias (intake assessed by questionnaire after diagnosis).
van Lee et al. (2011) (Australia): 577 cases of left-sided CRC, 277 cases of right-sided CRC, and 958 age- and sex-matched controls from the Western Australian Bowel Health Study (recruited between 2005 and 2007); 59−61% men; mean ages of cases and controls were 64.94 and 64.60 yr, respectively.	Intake was assessed by FFQ (74 items) modified to assess diet 10 yr earlier. Content estimates were obtained from Australian Food Composition Tables. Energy-adjusted intakes: Mean = 1,606.9 mg P/d. Quintile cut points = <1,335.29, <1,467.33, <1,606.80, <1,755.84, and ≥1,755.84 mg P/d.	Eligible cases had incident diagnosis of adenocarcinoma of the colon or rectum reported to the Western Australia Cancer Registry between 2005 and 2007. Tumor site was verified by review of histology reports in the Registry. Controls were obtained from random sample of the electoral roll in the area, and frequency matched to age and sex.	P intake was associated with a decreased risk of colorectal cancer (adjusted OR = 0.78, 95% CI = 0.58−1.05 for highest quintile compared with lowest; *p* for trend = 0.016). When stratified by location, the association was more evident for right-sided cancers than for left-sided cancers. Covariates in final model: Sex, age, BMI, smoking, cholecystectomy, alcohol consumption, SEIFA, and aspirin use.	Strengths: Large size. Limitations: Potential for recall bias (intake assessed by questionnaire after diagnosis).

[a]Nutrient databases in general are believed to underestimate P intake [as reviewed by McClure et al. (2017); EFSA (2015)]; this is a limitation of all the dietary studies.

BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; FFQ = food frequency questionnaire; OR = odds ratio; P = phosphorus; SEIFA = Socio-Economic Indexes for Areas.

2.1.2. Inhalation Exposures

Two occupational health studies with potential relevance to the hazard assessment of inhaled inorganic phosphates were identified: Khelifi et al. (2014) examined a small group of phosphate mine workers, and Yiin et al. (2016) evaluated mortality in phosphate fertilizer plant workers. Neither of these studies included any quantitative or qualitative estimates of exposure to airborne inorganic phosphates. Both populations likely had substantial exposure to other hazardous substances; Yiin et al. (2016) noted the following coexposures common to phosphate mining and processing: uranium and radon daughters; sulfuric acids and acid mists; inorganic mists containing sulfate, fluoride, and ammonium; and aerosols containing technically enhanced naturally occurring radioactive materials (TENORMs). Some of the workers at the phosphate fertilizer plant evaluated by Yiin et al. (2016) had been involved in uranium extraction during the 1950s. Khelifi et al. (2014) reported that phosphate miners were also exposed to silica dusts and often exhibited silicosis.

Khelifi et al. (2014) reported significantly higher white blood counts and serum levels of inflammatory markers (including IL-1β, IL-6, IL-8, MIP-1β, and LTB-4) in 12 male Tunisian phosphate mine workers, when compared with levels in 8 unexposed male controls. The effects were more pronounced in the subset of workers who smoked (data not shown). Yiin et al. (2016) observed significantly increased standardized mortality ratios (SMRs) for all-cause mortality (SMR = 1.07, 95% CI = 1.02−1.13), all-cancer mortality (SMR = 1.16, 95% CI = 1.06−1.28), lung cancer (SMR = 1.32, 95% CI = 1.13−1.53), and leukemia (SMR = 1.74, 95% CI = 1.11−2.62) in a cohort of 3,199 workers at a Florida facility producing phosphate fertilizers (data not shown). However, due to the potential coexposures and lack of qualitative or quantitative phosphate exposure estimates, it is not possible to ascertain the potential contribution of inorganic phosphates to the observed effects.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

The database of animal studies used to examine effects of oral intake of Na/K salts of inorganic phosphates is substantial and highly varied. To prioritize studies for consideration in the dose-response assessment, the following criteria were used to select the most relevant studies:

1) The experimental animal was a common laboratory species for toxicology studies (i.e., rat, mouse, hamster, rabbit, guinea pig, dog, monkey). Studies of pigs, cows, sheep, and cats were not considered.
2) A suitable control/referent group was included.
3) The phosphate compound administered and the dose(s) (either in terms of compound or in terms of P) were clearly and unambiguously reported.
4) Experimental animals used in the study were not genetically modified or pretreated to induce a disease or injured state.
5) Report or publication is in English. Studies reported in foreign languages but with an English abstract, tables, or summary in a secondary source are discussed briefly in Section 2.3.2.

6) Concentrations of P and Ca in the baseline diet administered to the referent or "control" and comparison groups were reported. The P data are necessary to ensure that the total phosphate dose can be accurately characterized, and the Ca data are needed to evaluate potential effects of altered Ca:P ratio, since Ca and P are coordinately controlled, and Ca content influences P absorption and excretion. Studies that did not provide the concentrations of Ca in the diet or did not report P concentration in the referent/control group, are discussed in Section 2.3.2.
7) At least two exposure groups received diets with Ca and P levels that met minimum nutritional requirements. As Ca and P are essential nutrients, intake below requirements can result in health effects. P and Ca requirements[1] for rats (3−3.7 g P/kg diet and 5−6.3 g Ca/kg diet and) and guinea pigs (4 g P/kg diet and 8 g Ca/kg diet) were obtained from NRC (1995). For studies in which the group reported as the control received P or Ca below nutritional requirements, other exposure groups were examined to determine whether another group could be designated as the referent group. In these instances, quantitative health outcome information was reanalyzed for statistical significance by comparing the exposure group(s) to the designated referent group.
8) Ca intake was constant across the referent/control and all relevant exposure groups. This requirement ensures any health outcomes observed can be attributed to changes in P dose alone.

Appendix A provides a flow chart showing the disposition of animal studies from the literature searches. In addition to the literature search results, the 2015 Cosmetic Ingredient Review (CIR) *Safety assessment of phosphoric acid and simple salts as used in cosmetics*, EFSA (EFSA, 2015, 2005), OECD SIDS Initial Assessment Reports for phosphoric acid and dipotassium hydrogen phosphate (K_2HPO_4) (OECD, 2009, 2006), and published reviews by Willhite et al. (2013) and Weiner et al. (2001) were consulted for animal studies on the subject of monovalent (specifically sodium or potassium) salts of inorganic phosphates, including unpublished studies.

Short-Term Studies

Hitchman et al. (1979)

In a study designed to evaluate nephrocalcinosis, female weanling Wistar rats (8/group) were administered diets containing 0.2−1% P and 0.5 or 1% Ca for 6 weeks. Because the minimum Ca and P requirements for rats are 0.5−0.63% (5−6.3 g Ca/kg diet) and 0.3−0.37% (3−3.7 g P/kg diet), respectively (NRC, 1995), only the groups administered 0.5% P (as calcium phosphate; designated as referent group) or 1% P (as a mixture of $CaHPO_4$ and NaH_2PO_4; designated treated group) and 0.5% Ca (both groups) were considered for this analysis. The proportions of calcium phosphate and NaH_2PO_4 administered to the treated group were not reported, but assuming that the additional phosphate in this group was derived from NaH_2PO_4 is reasonable. Based on reference food consumption (0.0164 kg/day) and body weight (0.156 kg) for female Wistar rats in a subchronic study (U.S. EPA, 1988), 0.5 and 1% in the diet are equivalent to approximately 530 and 1,100 mg P/kg-day. At sacrifice, kidneys were weighed and

[1]A definitive reference for Ca and P requirements in rabbits was not located, as discussed further in the summary of the Ritskes-Hoitinga et al. (2004) rabbit study.

analyzed for P and Ca content. Kidney histopathology was examined (dose groups were not specified).

In rats treated at 1,100 mg P/kg-day for 6 weeks, the study authors reported that renal Ca concentrations and kidney weights were significantly higher than in the 530 mg P/kg-day group (by 6.3-fold and 16%, respectively; $p < 0.05$ based on a two-sided *t*-test performed for this review) (see Table B-1) (Hitchman et al., 1979). The study authors noted "severe renal calcification" in rats administered 1,100 mg P/kg-day (presumably based on Ca concentrations only; histopathological results for this dose group were not reported). A LOAEL of 1,100 mg P/kg-day is identified based on increased kidney weights and kidney Ca levels in female rats. The LOAEL of 1,100 mg P/kg-day corresponds to a LOAEL (human equivalent dose [HED]) of 240 mg P/kg-day.[2]

Huttunen et al. (2007)

Effects on bone development were evaluated in male Wistar rats (10/group; 1 month old at study initiation) administered 0.6 (referent), 1.2, or 1.8% inorganic phosphate in the diet for 8 weeks. The diet of all groups of rats (including referents) contained 20.21% $CaHPO_4$ (as the only source of Ca; constituting 0.6% of the total diet). The diets of the 1.2- and 1.8%-groups were created by adding 14.5 and 40.9% monopotassium phosphate (KH_2PO_4), respectively, to the referent diet. Measured food consumption reportedly was 0.0184, 0.0177, and 0.0164 kg/day for the referent, 1.2-, and 1.8%-groups, respectively. Based on the food consumption above and reference (U.S. EPA, 1988) body weights (0.217 kg) for male Wistar rats, the U.S. EPA estimates that the concentrations of 0.6, 1.2, and 1.8% in the diet are equivalent to approximately 510, 980, and 1,400 mg P/kg-day.[3] Actual body-weight data were not presented in the published study.

The study authors estimated food consumption on the basis of the weight of leftover food; animals were offered 0.020 kg food/day, consistent with reference value food intakes for rats (U.S. EPA, 1988). Although the results section of the study states that total food consumption over the course of the 8-week study was 10.3, 9.9, and 9.2 kg for the referent, 1.2-, and 1.8%-groups, respectively, these values translate to the daily consumption rates (in kg/day) reported in the paragraph above around 10-fold greater than 0.020 kg/day; therefore, the total food intakes reported in the study were apparently mistakenly inflated 10-fold, and the true values were actually 1.03, 0.99, and 0.92 kg, respectively. These values were divided by 56 days to get the daily food consumption rates used in the dosimetry calculations.

Body weights were measured four times during the study (Days 0, 28, 42, and 52). After 8 weeks, blood was collected to evaluate serum Ca, P, and PTH concentrations. Prior to study initiation and at study termination, right femur bone area, bmc, and bmd were measured using dual-energy x-ray bone densitometry (DXA). Bone labeling (with tetracycline) was performed 12 and 2 days prior to sacrifice; labeling was used to measure mineral apposition rate (MAR) in

[2]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 240 mg/kg-day using a dosimetric adjustment factor (DAF) of 0.22 (HED = adjusted daily dose [ADD] × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data for rats (0.156 kg) and reference body weights for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

[3]Reported dietary intakes (% P in food) were converted to ADDs using the following equation: ADD = (% P in food × 10,000 [mg P/kg food] × food intake [kg food/day]) ÷ average body weight.

longitudinal frontal sections of the distal (left) femur. Left femurs were subsequently processed for histomorphometry (measurements of trabecular bone area, total trabecular perimeter, trabecular width, osteoblast perimeter, and osteoclast count); right femurs were analyzed using peripheral quantitative computed tomography (to measure bmd, bmc, and cross-sectional area [CSA] of total bone, trabecular bone, and cortical bone for the distal metaphysis and midshaft). The length of the right femur was measured; six right tibias were evaluated using microcomputed tomography (to evaluate the trabecular total volume, bone volume, and bone surface; trabecular separation and number, structure model index [SMI; a measure of plate:rod ratio in bone architecture], connective structures per unit volume, and degree of anisotropy; cortical cross-sectional area, thickness, and porosity). Right femoral necks and tibial shafts were subjected to mechanical testing (including measurements of strength, stiffness, toughness, and yield point).

Although the study indicated that 30 rats were randomized into three groups, tabular results are presented for 9 (rather than 10) referent group rats; no explanation was provided (Huttunen et al., 2007). Rats treated at 980 and 1,400 mg P/kg-day reportedly showed significant reductions in food consumption (4−11% lower than referent group) and body weights (reported by the study authors to be 11 and 29% lower than controls; data not presented numerically) over the course of the study.

The study authors reported that serum PTH (but not Ca or P) was significantly increased in 1,400 mg P/kg-day rats (sevenfold change relative to referent group). Based on DXA measurements, femur length was significantly decreased in rats treated at 1,400 mg P/kg-day (8% shorter than referent); rats treated at 980 and 1,400 mg P/kg-day showed decreased femur bmc or bmd (9−20% lower than referent; see Table B-2). Analysis of histomorphometric parameters showed trabecular-related endpoints (bone area, width, and perimeter) were significantly decreased (by about 27−72%), and osteoclast number and MAR were significantly increased (by about 1.4- to 3.3-fold) in treated rats compared with those in the referent group; these effects were dose-related (data were shown graphically).

In the distal metaphysis (of right femurs), the study authors reported that trabecular and cortical bmc and CSA were significantly decreased at 980 and 1,400 mg P/kg-day; changes were not strictly dose-related (see Table B-2). The study authors reported that these effects plus reductions in cortical bmd and thickness (3 and 10% lower than referents, respectively, at 1,400 mg P/kg-day) were seen in the midshaft. Analyses of (right) tibial bones showed that treatment significantly affected trabecular bone volume, bone surface, and SMI (all negatively) on the basis of analysis of variance (ANOVA) only; no post hoc analysis was performed. The study authors reported that the cortical cross-sectional area was significantly decreased. Mechanical testing of femurs (femoral neck) showed treatment at 1,400 mg P/kg-day significantly decreased strength and yield point (by 24 and 36%, respectively). The study authors reported that treatment negatively affected all parameters of mechanical competence in tibial shafts (on the basis of an ANOVA of strength, yield point, stiffness, and toughness). A LOAEL of 980 mg P/kg-day is identified on the basis of decreased body weight and effects on bone parameters (decreased femur bmd and alterations in bone structure) in rats treated for 8 weeks (a

NOAEL was not identified). The LOAEL of 980 mg P/kg-day corresponds to a LOAEL (HED) of 240 mg P/kg-day.[4]

Koshihara et al. (2005)

Female Wistar rats (5/group) were administered 0.5% (referent) or 1.5% inorganic phosphate (as KH_2PO_4) for 6 weeks. On the basis of average reported food-consumption (0.0136 kg/day) and body-weight (average of initial and final weights; 0.256 and 0.254 kg for referents and treated rats, respectively) data provided in the study, concentrations of 0.5 and 1.5% in the diet are equivalent to approximately 270 and 800 mg P/kg-day as calculated by the U.S. EPA. An additional group of rats was administered a low-phosphate diet (0.15% in the diet or approximately 74 mg P/kg-day). The composition of the diets otherwise remained constant (Ca was maintained at 0.5% of the diet). Food consumption and body weights were monitored (time points not specified). The feces and urine of all rats were collected for 3 days prior to study termination; the excretion of Ca, P, creatinine, or deoxypyridinoline (DPD; a marker of bone resorption) were quantified. Serum was collected at study termination to determine Ca, P, PTH, and osteocalcin (a marker of bone formation) concentrations. Fifth lumbar vertebra (L5) samples were also collected; bmc and bmd were measured, and compression load of L5 was determined.

Results for the 800 mg P/kg-day group were compared with the 270 mg P/kg-day group (as referent) (Koshihara et al., 2005). Food consumption and body weights were reported to be unaffected by treatment. The study authors reported that Ca absorption was significantly decreased (61% lower than referents), whereas P absorption and excretion (in the urine) were significantly increased (3.8- to 3.9-fold higher than referents; see Table B-3). No significant, treatment-related effects on serum concentrations of Ca, P, or PTH were observed; however, serum osteocalcin was 39% higher in rats treated at 800 mg P/kg-day compared with referents. The study authors reported that urinary excretion of DPD also was significantly elevated at 800 mg P/kg-day (27% higher than controls). Data from the low-phosphate (0.15%) group showed increased P absorption. Although bmc and the compression load of L5 were not significantly affected by treatment, the bmd in vertebrae of rats treated for 6 weeks decreased. The LOAEL of 800 mg P/kg-day is based on decreased bmd in vertebrae bmd that was significantly lower (by 8%) in 800 mg P/kg-day rats relative to referents. A LOAEL is identified on the basis of these data of 800 mg P/kg-day, which corresponds to a LOAEL (HED) of 200 mg P/kg-day.[5]

[4]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 240 mg P/kg-day using a DAF of 0.24 (HED = ADD × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data were not reported; therefore, reference body weights recommended by U.S. EPA (1988) were used to calculate the DAF: 70 kg for humans and 0.217 kg for male Wistar rats in a subchronic study.

[5]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 200 mg P/kg-day using a DAF of 0.25 (HED = ADD × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data for rats (0.254 kg) and reference body weights for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

Ritskes-Hoitinga et al. (1989)

Female Wistar RIV:TOX rats (6 or 16 females/group) were administered 0.4 (control) or 0.6% P (as NaH_2PO_4 dihydrate) in the diet for 28 days. The concentration of Ca in the diet remained constant (0.48−0.50%, administered as calcium carbonate). On the basis of measured food consumption (0.0119 and 0.0124 kg/day for the control and treated groups, respectively) and body weights (average of initial and final weights; 0.126 and 0.129 kg, respectively), 0.4 and 0.6% in the diet are equivalent to approximately 390 and 580 mg inorganic phosphate/kg-day (respectively). Food consumption was measured continuously, while body weights were measured at study initiation and at study termination. Data on water consumption, and urine or feces were collected on Study Days 0−2, 13−15, and 26−28; urine and feces were analyzed for P, Ca, and magnesium levels (Days 13−15 and 26−28). Serum was evaluated for creatinine, urea, and osmolality (Study Day 28); urine was evaluated for the same parameters as for volume, pH, and albumin (Study Days 0−2, 13−15, and/or 26−28). At sacrifice, kidney weights were recorded. The right kidney of each animal was homogenized and analyzed for P, Ca, and magnesium content. The left kidney, heart, liver, thoracic aorta, parathyroid, stomach, and lung were examined grossly and microscopically (hematoxylin and eosin [H&E] staining). Additional sections of the kidney, stomach, and lung were processed (using von Kossa staining) to detect P-containing deposits. The severity of nephrocalcinosis was scored on a scale of 0−3 (on the basis of the average scores of two blinded assessors).

No significant, treatment-related effects on food and water consumption or body weights were observed (see Table B-4) (Ritskes-Hoitinga et al., 1989). The study authors reported that urinary P excretion was significantly increased relative to controls on Study Days 13−15 and 26−28 (2.1- to 2.4-fold) (data not shown); magnesium retention was transiently increased (42% on Days 13−15 only). The study authors reported observing no significant changes in serum parameters; however, urine pH was significantly decreased (8−17% on Days 0−2, 13−15, and 26−28) and urinary albumin was significantly increased (1.8- to 2.8-fold on Days 13−15 and 26−28) at 580 mg/kg-day. Levels of urea in the urine were increased on Days 13−15 only (the toxicological significance was uncertain). At study termination, relative kidney weights were reported to be 27% higher in treated rats than in controls. Kidney concentrations of Ca, P, and magnesium also were reported to be significantly higher in treated rats; the magnitude of this effect was most pronounced for Ca (increased 14-fold, compared with about twofold for P and magnesium). Reported histopathological abnormalities were confined to the kidneys; deposits were seen in the cortex, corticomedullary junction, and papilla. Because deposits in the cortex and papilla were birefringent and showed no specific localization, the study authors considered them artifacts of the fixation process (likely caused by the dissolution of corticomedullary deposits). Therefore, only calculi in the corticomedullary area were factored into nephrocalcinosis scores. The reported incidence of nephrocalcinosis was 16/16 in rats treated at 580 mg/kg-day (mean severity = 2.7) compared with 2/6 in controls (mean severity = 0.5). The difference in the distribution of histological scores among groups was statistically significant ($p < 0.05$). Extreme cases of nephrocalcinosis reportedly were accompanied by interstitial fibrosis and focal tubuli with regenerated epithelia (incidence data not provided).

In a follow-up experiment designed to determine the time course of these effects (i.e., increased urine albumin and nephrocalcinosis), two additional groups of rats (12 females/group) were administered 0.4% (control) or 0.6% P (as NaH_2PO_4) in the diet for 28 days. The concentration of Ca in the diet remained constant (0.48−0.50%, administered as calcium carbonate). Based on measured food consumption (0.0125 and 0.0119 kg/day for the

control and treated groups, respectively) and body weights (average of initial and final weights; 0.126 and 0.124 kg, respectively), 0.41 and 0.61% in the diet are equivalent to approximately 410 and 590 mg P/kg-day (respectively). Food consumption was measured continuously, while body weights were measured at study initiation and at study termination. Urinary parameters (volume, pH, and albumin only) were evaluated from samples collected on Study Days 0−2, 13−15, and 26−28. Serum determinations (of P, Ca, and magnesium) were conducted on six rats/group prior to sacrifice on Study Days 14 and 28. Relative kidney weights were recorded. Kidney P, Ca, and magnesium concentrations were measured. Histopathological examinations were performed (kidneys, parathyroid, stomach, and lungs).

No significant, treatment-related effects on food and water consumption or body weights were observed (see Table B-5) (Ritskes-Hoitinga et al., 1989). The study authors reported that urinary pH was significantly decreased at all time points (7−10%); urine albumin was increased 1.7- to 3.4-fold on Study Days 13−15 and 26−28 (after an initial decrease on Days 0−2); effects were reported to be statistically significant on Study Days 0–2 and 13–15. Serum P was reportedly not significantly affected by treatment, but serum Ca and magnesium levels were significantly reduced in treated rats relative to controls (by 6 and 18%, respectively). Although not statistically significantly increased, the study authors reported that relative kidney weights in rats treated at 580 mg/kg-day were 24% higher than controls by Day 28, which is considered by this review to represent a biologically significant change. In general, kidney concentrations of Ca, P, and magnesium were significantly increased except P on Day 28, with the effect on Ca being most pronounced (at least fourfold higher than controls). Most rats (treated group and controls) showed evidence of nephrocalcinosis (Days 14 and 28); however, the distribution of severity scores among groups was statistically significantly different (i.e., more severe at 580 mg/kg-day). The study authors observed mineral deposits at the corticomedullary junction only, and, unlike Experiment 1, no deposits occurred in the cortex or papilla (the study authors attributed the cortical and papillary deposits seen in Experiment 1 to be artifacts of fixation with Bouin's solution, and Experiment 2 used formalin for fixation). As in Experiment 1, the study authors reported that severe nephrocalcinosis cases showed interstitial fibrosis and tubular epithelial regeneration. No other histopathological effects were reported. A LOAEL of 580 mg/kg-day is identified on the basis of the data from these two experiments for kidney effects (increases in urine albumin and relative kidney weights; evidence of nephrocalcinosis). The LOAEL of 580 mg/kg-day corresponds to a LOAEL (HED) of 120 mg/kg-day.[6]

Ritskes-Hoitinga et al. (2004)

In a study designed to more rigorously determine the optimal dietary P concentration for rabbits, New Zealand White (NZW) rabbits (eight males/group) were administered P (as NaH_2PO_4 dihydrate) at four nominal dietary concentrations (0.1, 0.2, 0.4, and 0.8% P in the diet) for 8 weeks. As noted by the study authors, few data on the P requirements of rabbits are available. NRC (1977) recommended 0.22% P in diet, for growth, with higher requirements (0.37−0.5%) for pregnant or lactating rabbits; these values were based on studies using predominantly natural diets in which P bioavailability may have been limited. Clarke et al. (1977) recommended a P concentration of 4 g P/kg diet (0.4%) and Ca concentration of 5 g

[6]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 120 mg/kg-day using a DAF of 0.21 (HED = LOAEL × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data for rats (0.129 or 0.124 kg) and reference body weights for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

Ca/kg diet (0.5%) for laboratory rabbits but cited no published sources as the basis for these recommendations.

Diets used by Ritskes-Hoitinga et al. (2004) contained relatively constant Ca concentrations of 0.45−0.46%. Clarke et al. (1977) recommended a minimum concentration of 5 g Ca/kg diet (0.5%) for laboratory rabbits, but with no supporting citations. NRC (1977) suggested that dietary Ca needs in rabbits depend on dietary P, citing data suggesting that at a dietary P level of 0.37%, optimal growth was achieved at 0.22% Ca, but optimal bone calcification required 0.34−0.40% Ca (suggesting a Ca:P ratio requirement of ~1). NRC (1977) further noted that in rabbits, serum Ca levels generally correspond to dietary Ca intake; in contrast, serum Ca is regulated within a narrow range in other mammalian species. Ritskes-Hoitinga et al. (2004) concluded on the basis of their experiments 0.2% should be a maximum dietary P level for rabbits, based on increasing incidences of renal calcifications.

In the absence of a definitive minimum dietary P requirement for rabbits, and evidence that Ca and P requirements appear to be interdependent in this species, the referent group selected by the study authors for this study was the concentration that provided an approximate Ca:P ratio of 1:1 (i.e., 0.4% P). This group also had Ca and P intakes corresponding to the recommendations of Clarke et al. (1977).

Measured concentrations of P in the referent and exposed group diets were 0.45 and 0.88%, respectively. On the basis of measured food consumption (0.0731 and 0.0689 kg/day for the referent and treated groups, respectively) and body weights (average of initial and final weights; 2.22 and 2.09 kg, respectively), 0.45 and 0.88% P in the diet are equivalent to approximately 150 and 290 mg P/kg-day as calculated by the U.S. EPA. Food consumption (based on the weight of leftover food) and body weights (initial and final) were recorded. Phosphorus, Ca, and magnesium concentrations in the urine and feces were measured from samples collected on Study Days 20−23 and 48−51; levels in the serum were quantified on Study Days 28 and 56. At sacrifice on Day 57, right kidney weights were recorded; kidneys were analyzed for P, Ca, and magnesium content. Left kidneys were subjected to histopathological examinations (H&E and von Kossa staining); the severity of nephrocalcinosis in the cortex and the medulla was graded on a scale of 0 (absence of nephrocalcinosis) to 3 (severe nephrocalcinosis). Femur parameters (volume, length, circumference) were evaluated; two parts of the femur (the medial diaphysis and the epiphysis) were also processed for mineral content.

No significant, treatment-related effects on food consumption or body weights were observed among rabbits administered 150 and 290 mg P/kg-day (Ritskes-Hoitinga et al., 2004). The study authors observed numerous effects on mineral balance win rabbits treated at 290 mg P/kg-day (see Table B-6); changes consistently observed on Study Days 20−23 and 48−51 were decreased urinary pH (8.04 vs 9.35 at the latter time point) and decreased Ca (25- to 34-fold) and increased P (2.2- to 3.3-fold) in the urine. The study authors reported that serum P, but not serum Ca or magnesium, was significantly increased on Study Days 28 and 56 in rats treated at 290 mg P/kg-day (17.9−19.7% higher than referents). The study authors reported that kidney weights (absolute and relative) were not statistically significantly affected by treatment; however, concentrations of Ca and P in the kidney were increased (Ca statistically) at 290 mg P/kg-day (412 and 29.2% higher than referents, respectively); these effects were considered by the study authors to be indicative of nephrocalcinosis. In agreement, histopathological evaluations showed significantly increased incidence and severity scores for cortical calcifications using both

staining methods (differences in calcinosis were not observed in the medulla). At 150 and 290 mg/P/kg-day, the incidence of any calcification (i.e., severity scores 1–3) in the cortex was 2/6 vs. 8/8 with H&E staining and 3/8 vs. 8/8 in the von-Kossa-stained group. The study authors noted that femur parameters were not significantly affected, other than significantly increased magnesium content in both the medial diaphysis (14−16% higher than referents) and epiphysis (26% higher than referents). A LOAEL of 290 mg P/kg-day is identified on the basis of histological evidence of nephrocalcinosis in rabbits. The LOAEL of 290 mg P/kg-day corresponds to a LOAEL (HED) of 120 mg P/kg-day.[7]

Tani et al. (2007)

Wistar rats (six males/group) were administered P (as KH_2PO_4) at 0.3 (control), 0.6, 0.9, 1.2, or 1.5% in the diet for 4 weeks. On the basis of measured food consumption (0.015−0.018 kg/day, calculated by dividing the reported 4-week intakes by 28 days) and reference body weights for male Wistar rats (0.217 kg) (U.S. EPA, 1988), concentrations of 0.3, 0.6, 0.9, 1.2, and 1.5% in the diet are equivalent to approximately 250, 450, 670, 920, and 1,000 mg P/kg-day. The composition of the diets otherwise remained constant (Ca was maintained at 0.6% of the diet). Food consumption and body weights were measured twice weekly. Urine and feces were collected on the last 3 days of study to evaluate Ca and P content. At study termination, blood was collected to measure serum levels of Ca, P, PTH, and vitamin D. Kidney samples were attained to determine messenger ribonucleic acid (mRNA) (total kidney) and protein (in brush border membrane vesicles of the renal cortex) levels of the sodium-dependent phosphate transporter (Npt IIa).

Food consumption was significantly decreased in all groups of treated rats relative to the referent group (8−17% lower than referents and not strictly dose-related; Table B-7) (Tani et al., 2007). Body weights were not reported, but, according to the study authors, body-weight gain (over the course of 4 weeks) was significantly decreased at 670 and 1,000 mg P/kg-day (but not 920 mg/kg-day); body-weight gain was only 62% of referent values at 1,000 mg P/kg-day. Body-weight gain expressed per 100 g of food intake was significantly decreased at 1,000 mg P/kg-day only (26% lower than referents). Tani et al. (2007) reported that urinary (at ≥450 mg P/kg-day) and fecal (at ≥670 mg P/kg-day) excretion of P was significantly increased in a dose-related manner; net absorption also increased with dose (5.4-fold higher than in referents at the 1,000 mg P/kg-day dose). Urinary (but not fecal) excretion of Ca was significantly affected (decreased at ≥450 mg/kg-day), according to the study authors; net absorption was decreased only at 1,000 mg P/kg-day only (7.4-fold lower than referents). Tani et al. (2007) reported that levels of Ca and P in the serum were not significantly altered by treatment. Although PTH levels tended to be increased in all treatment groups, the study authors reported that serum PTH was significantly increased only at 1,000 mg P/kg-day (9.6 times higher than in referents). Vitamin D levels were significantly increased at 670 mg P/kg-day only (and not at higher doses) (Tani et al., 2007). The study authors also reported that expression of Npt IIa was markedly decreased at 1,000 mg P/kg-day; mRNA and protein levels were 57 and 21% of referent levels, respectively (data not shown). NOAEL and LOAEL values of 920 and 1,000 mg P/kg-day, are identified respectively, based on decreased body-weight gain and body-weight gain normalized to intake.

[7]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 120 mg P/kg-day using a DAF of 0.42 (HED = LOAEL × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data for rabbits (2.09 kg) and reference body weights for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

The NOAEL and LOAEL of 920 and 1,000 mg P/kg-day correspond to NOAEL (HED) and LOAEL (HED) values of 220 and 240 mg P/kg-day, respectively.[8]

Subchronic toxicity studies

Abuduli et al. (2016)

In a study designed to assess effects on glucose and lipid metabolism, male Sprague Dawley rats (six/group) were administered 0.6% (referent) or 1.2% inorganic phosphate (as 2.53 or 5.17% KH_2PO_4 in the diet, respectively) for 4 or 14 weeks. Based on reference (U.S. EPA, 1988) food consumption (0.0234 kg/day) and body weight (0.267 kg) for male Sprague Dawley rats in a subchronic study (food consumption and body-weight data from the study were not presented numerically), concentrations of 0.6 and 1.2% in the diet are equivalent to approximately 530 and 1,100 mg P/kg-day. An additional group of rats was administered a low-phosphate diet (0.2% in the diet or approximately 180 mg P/kg-day). The composition of the diets otherwise remained constant (Ca was maintained at 0.6% of the diet).

Rats treated for 14 weeks were evaluated for food consumption (measured every other day), body weights (measured daily), and liver triglycerides only. In rats administered inorganic phosphate for 4 weeks, food consumption and body weights were recorded regularly. Fat deposits were measured and categorized as epididymal (eWAT), mesenteric (mWAT), or retroperitoneal (rpWAT) white adipose tissue (WAT). Oxygen consumption (V_{O2}) and carbon dioxide production (V_{CO2}) were evaluated continuously at 10-minute intervals over a 3-day period; the respiratory quotient (RQ; the ratio of O_2 consumption to CO_2 production) was calculated. Locomotor activity was measured over a 24-hour period (using an infrared-based device). Glucose tolerance tests (to measure serum glucose and insulin levels before and after administration of a bolus dose of glucose) were performed after 3 weeks of treatment; the homeostasis model assessment of insulin resistance (HOMA-IR) was determined on the basis of fasting glucose and insulin concentrations.

Prior to terminal sacrifice, blood was collected to evaluate biochemical or clinical chemistry parameters, including P and Ca levels; creatinine and blood urea nitrogen (BUN), total cholesterol and triglycerides, leptin and adiponectin levels, nonesterified fatty acids (NEFA), 1,25-dihydroxy-vitamin D3, and the concentrations of PTH, FGF-23, triiodothyronine (T_3), or thyroxine (T_4); hepatic lipids were also isolated to measure total cholesterol and triglyceride levels. Selected tissues were weighed (liver, kidney, heart, muscle, and brown adipose tissue (BAT); interscapular fat, white adipose tissue (WAT) and BAT were examined histologically (H&E staining). RNA was extracted from the liver, BAT, and WAT to assess gene expression related to lipogenesis and lipolysis. Three additional groups of male rats were administered the experimental diets for 4 weeks to evaluate metabolic activity in the BAT (measured as [^{18}F]-fludeoxyglucose [FDG] uptake).

[8]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, 2011b), the NOAEL and LOAEL were converted by the U.S. EPA to HEDs of 220 and 240 mg P/kg-day using a DAF of 0.24 (HED = LOAEL × DAF). The DAF was calculated as follows: $DAF = (BW_a^{1/4} \div BW_h^{1/4})$. Reference body weights for male Wistar rats (0.217 kg) and humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

Results for the 1,100 mg P/kg-day group are compared with the 530-mg P/kg-day group only (as referent) (Abuduli et al., 2016). In rats evaluated after treatment for 4 weeks, the study authors observed no significant treatment-related effects on body weight (see Table B-8). However, the study authors reported that rats treated at 1,100 mg P/kg-day showed decreased visceral fat accumulation (mWAT and rpWAT content were about 25% lower than in referents, based on data presented graphically). No significant differences in V_{O2} or V_{CO2} were observed, however, the RQ was lower in the 1,100-mg P/kg-day group than in referents (slightly but significantly affected during the dark cycle only; <10% lower based on visual inspection of data presented graphically) (Abuduli et al., 2016). The study authors reported that locomotive activity was similar among groups. No significant differences between the referent group and the 1,100-mg P/kg-day group were observed with respect to blood glucose levels, fasting blood glucose, or insulin levels, or HOMA-IR. The administration of a diet containing 1,100 mg P/kg-day did not significantly alter the levels of P, Ca, creatinine, cholesterol or triglycerides, 1,25-dihydroxy-vitamin D3, adiponectin, or thyroid hormones in the blood (Abuduli et al., 2016). However, rats treated at 1,100 mg P/kg-day showed significantly increased blood levels of BUN (32% higher than referents) and PTH (~6 times higher than referents), and significantly decreased leptin (~15% lower than referents based on data presented graphically) and NEFA (28% lower than referents) (Abuduli et al., 2016); see Table B-8. FGF-23 levels tended to be increased at 1,100 mg P/kg-day (77% higher than referents), but this effect was not statistically significant according to the study authors. Liver cholesterol and triglycerides were also reported to be unaffected by treatment.

Although the study authors observed no significant differences in food consumption throughout the 14-week study period, rats administered 1,100 mg P/kg-day in the diet showed decreased body weights from Week 8 onward (up to approximately 14% lower than referents, based on data presented graphically). Likewise, lower liver triglyceride levels were observed in rats treated at 1,100 mg P/kg-day (1.36 ± 0.35 mg/g in the high-phosphate group compared with 2.57 ± 0.51 mg/g in referents; the study authors' statistical analyses were based on comparison to the 180 mg P/kg-day group only; number of animals not reported for independent analysis). Decreased triglycerides in 1,100 mg P/kg-day rats is not considered a toxicologically relevant effect. A LOAEL of 1,100 mg P/kg-day is identified based on decreased body weights in rats administered inorganic phosphate in the diet for 14 weeks. A NOAEL cannot be identified as the next lowest dose is the referent dose. The LOAEL of 1,100 mg P/kg-day corresponds to a LOAEL (HED) of 270 mg P/kg-day.[9]

No statistically significant effects on organ weights occurred based upon inspection of the data presented graphically; however, on the basis of the data contained in the study report, kidney weights were approximately 12% higher (based on data digitized using GrabIt™) in rats treated at 1,100 mg P/kg-day relative to the referent group, which is considered biologically relevant. Histological analysis showed decreased lipid content in BAT of rats administered 1,100 mg P/kg-day. In the liver and WAT, no statistically significant changes in gene expression were observed; however, the expression of genes related to lipid oxidation (namely uncoupling

[9]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 270 mg P/kg-day using a DAF of 0.25 (HED = LOAEL × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data were not reported; therefore, reference body weights recommended by U.S. EPA (1988) were used to calculate the DAF: 70 kg for humans and 0.267 kg for male Sprague Dawley rats in a subchronic study.

protein 1 [UCP1] and peroxisome proliferator-activated receptor-γ coactivator-1α [PGC-1α]) was significantly increased in BAT of rats treated at 1,100 mg P/kg-day relative to referents. No significant differences in [^{18}F]-FDG uptake were noted among treatment groups. Effects on lipid metabolism (e.g., reduced fat accumulation) were not considered toxicologically relevant by the U.S. EPA. However, a LOAEL of 1,100 mg P/kg-day is identified for the 4-week study on the basis of evidence of kidney effects (increases in BUN and kidney weight). The administered dose of 1,100 mg P/kg-day corresponds to an HED of 270 mg P/kg-day.

Datta et al. (1962)

Birmingham-Wistar rats (20/sex/group) were administered inorganic phosphate as $Na_4P_2O_7$ (97.5% with 2.5% orthophosphate) at 0 (referent), 1, 2.5, or 5% in the diet for 16 weeks. The test material was also reported by the trade name, Tetron K; however, the specific forms of sodium phosphates corresponding to the reported material could not be determined. Analysis of the diet showed P constituted 0.526% of the referent diet and 1.65% of the high-dose diet, so these values were used to calculate doses. The P contents of the 1 and 2.5% diets were not provided; therefore, doses (in mg P/kg-day) cannot be reliably estimated for these groups. The concentration of Ca in the diets was relatively constant (0.45−0.64% of the diet). Based on data provided in the study report for food consumption (0.0117 and 0.0106 kg/day for referent males and females, respectively, and 0.0108 and 0.0094 kg/day for 5% males and females, respectively; calculated by dividing total intakes reported by study authors by 112 days) and mean body weights (0.220 and 0.159 kg for referent males and females, respectively, and 0.209 and 0.147 kg for 5% males and females, respectively; calculated as average of initial and final weights, assuming initial body weight of 115 g for males and 90 g for females on the basis of range reported by study authors), U.S. EPA estimates that 0.526% P in the diet is equivalent to approximately 280 mg P/kg-day (males) and 350 mg P/kg-day (females), and 1.65% P in the diet is equivalent to approximately 860 mg P/kg-day (males) and 1,100 mg P/kg-day (females). An additional group of rats (20/sex) was administered 5% Na_2HPO_4; P composed 1.598% of that diet. Based on food consumption (0.0122 and 0.0104 kg/day for males and females, respectively) and mean body weights (0.232 and 0.160 kg for males and females, respectively), 1.598% P in the diet is equivalent to approximately 840 mg P/kg-day (males) and 1,000 mg P/kg-day (females).

In each dose group, 10 rats/sex were housed individually; remaining rats were grouped 5 per cage. Food consumption and body weights were recorded weekly (for rats housed individually only) for the first 100 days (about 14 weeks) of the study. Urine and feces were collected after 3 weeks (five referent males and five males treated with 5% $Na_4P_2O_7$) and 8 weeks (five males each from the 5% $Na_4P_2O_7$ and orthophosphate groups); levels of Ca, phosphate, and pyrophosphate were measured. Urine was also analyzed for pH, and for sodium, potassium, and ammonium concentrations. At study termination, hematology parameters (red blood cell [RBC] and differential white blood cell [WBC] counts; hemoglobin [Hb]) were examined in five rats/sex/group. Liver function (based on bromosulphalein [BSP] clearance) and kidney function (phenol red excretion test, concentration test, albumin, and cellular contents) were evaluated in five rats/sex/group after 110 days. At sacrifice, organ weights (of the heart, liver, spleen, stomach, intestines, adrenals, kidneys, and testes) were recorded; rats were subjected to gross and microscopic examinations (10 rats/sex/group that were housed individually; tissues not specified).

Results are summarized in Table B-9. In groups exposed to $Na_4P_2O_7$, the study authors reported reduced food consumption and body-weight gain in rats receiving 5%; but only body-weight gain in females was statistically significantly lower compared with the referent group (Datta et al., 1962). Additional statistical analyses (covariance using the method of Crampton) showed food consumed per unit of body-weight gain was similar between the 5% $Na_4P_2O_7$ group (both sexes) and referents (data not shown). Ca absorption and excretion were similar among (male) rats treated with 5% $Na_4P_2O_7$ and referents, but the percentage of phosphate excreted in the urine was markedly increased (Datta et al., 1962). The study authors reported that other than urinary pH (7.5 in the both the pyrophosphate and Na_2HPO_4 5%-groups, compared with 6.7 in referents), urinary endpoints were unaffected by treatment. Pyrophosphate was not detected in the urine or feces of treated animals, suggesting pyrophosphate was hydrolyzed to orthophosphate prior to or after absorption.

The study authors observed no hematological effects considered toxicologically relevant in groups exposed to the pyrophosphate, and BSP clearance was unaffected by treatment. Although no significant effects were observed on other tests of kidney function, the concentration test showed significantly decreased urine specific gravity in the 2.5%- and 5%-groups in males and the 5%-group in females (Datta et al., 1962). Relative kidney weight was significantly increased in female rats treated with 2.5 and 5% $Na_4P_2O_7$ (24 and 49% higher than referents, respectively) and in males exposed to 5% (21% higher) (Datta et al., 1962). Rats treated at 5% $Na_4P_2O_7$ (860 mg P/kg-day for males and 1,100 mg P/kg-day for females) also showed significantly increased relative heart (12−21% higher than referents), stomach (~60% higher), and testes (28% higher) weights; intestinal weight was increased in females only (27% higher) (Datta et al., 1962). The study authors noted an apparent increased incidence (although not statistically significant) of gross pathological changes in the stomach of female rats treated with 2.5 and 5% $Na_4P_2O_7$ (hypertrophy and hemorrhage); gross kidney effects (pale kidneys and calcification) were also noted in these groups. In males, increased incidence of histological effects were only seen in the 5%-groups (Datta et al., 1962). Histopathological changes were confined to the kidney, and (on the basis of data for the combined sexes) included significantly increased incidences of hemorrhages and exudate (all treatment groups); medullary calcification (2.5- and 5%-groups); and medullary necrosis, tubular casts, and chronic inflammation (5%-groups only) (Datta et al., 1962). Cortical effects noted in the study report (atrophy, hyaline degeneration, and calcification) were not dose-related. The study report noted that no histopathological changes were observed in the stomach. Because effects in rats administered phosphate as pyrophosphate occurred at doses that could not be quantified, no effects levels are identified for the pyrophosphate experiment.

In the group exposed to Na_2HPO_4, no treatment-related change in Ca absorption or excretion was seen, but the urinary excretion of P was markedly increased (Datta et al., 1962). As noted above, the urinary pH was higher in the Na_2HPO_4 exposed group than in referents (7.5 compared with 6.7 in referents), while other urinary parameters did not differ. Exposure to Na_2HPO_4 resulted in slightly, but statistically significantly increased RBC count in females but not males (Datta et al., 1962). The study authors reported that hemoglobin was slightly (6%) but statistically significantly increased in both sexes. BSP clearance was unaffected by treatment (Datta et al., 1962). As with the pyrophosphate, exposure to Na_2HPO_4 resulted in significantly decreased specific gravity in the concentration test in both sexes, while other kidney function tests showed no significant effects(Datta et al., 1962). Significantly increased relative kidney weight was observed by the study authors in Na_2HPO_4-treated rats of both sexes (17−39% higher

than referents). Increased incidence of gross changes were not statistically significant and were observed only in the kidney and consisted of pale kidneys and macroscopically observed calcification. Increased incidences (both sexes combined) of renal damage, hemorrhages and exudate, chronic inflammation, medullary calcification, medullary necrosis, and tubular casts were reported (Datta et al., 1962). A LOAEL of 840 mg P/kg-day is identified for males on the basis of evidence of kidney effects (changes in specific gravity, increased relative kidney weight, gross or microscopic evidence of kidney damage); a NOAEL could not be established as there were effects at all calculable doses above referent. The LOAEL of 840 mg P/kg-day corresponds to a LOAEL (HED) of 200 mg P/kg-day.[10]

Dymsza et al. (1959)

Male Wistar rats (up to 12/group) were administered a referent diet (0.87% K_2HPO_4, with P comprising 0.43% of the total diet) for up to 150 days. Additional groups of rats received diets containing "normal" orthophosphate (0.87% K_2HPO_4 and 0.43% P) or "high" orthophosphate (5.1% K_2HPO_4 and 1.3% P), "normal" metaphosphate (0.93% $[NaPO_3]_6$ and 0.46% P), or "high" metaphosphate (3.5% $[NaPO_3]_6$ and 1.2% P). Other components of the diet were held relatively constant (Ca comprised 0.47−0.56% of the diet). Differences occurred between the referent and normal ortho- and metaphosphate diets unrelated to phosphate administration; the normal ortho- and metaphosphate diets contained 5−6% more mineral salts (not further characterized) and higher sodium and chlorine concentrations. Based on measured food consumption (ranging from 0.01825 to 0.0200 kg/day; calculated by dividing 60-day intakes reported by study authors by 60 days) and body weights (ranging from 0.190 to 0.202 kg; calculated as average of initial and final weights, assuming initial body weight of 55 g for males on the basis of range reported by study authors) for the first 60 days of the study, these concentrations in the diet are equivalent to approximately 380 (referent), 420 (normal K_2HPO_4), 1,100 (high K_2HPO_4), 470 (normal $[NaPO_3]_6$), or 1,100 (high $[NaPO_3]_6$) mg P/kg-day. Food consumption and body-weight gain were recorded (time points not specified); food and protein efficiency were calculated. After 50 days of the study, 7-day Ca and P balance studies were conducted using nine rats/group (by comparing the amounts consumed to amounts excreted in the feces and the urine). After 60 days on the test, five rats/group were sacrificed. Hematological (Hb concentration) and clinical chemistry (serum levels of Ca and P) parameters were evaluated. The remaining animals (6 or 7/group) were kept on the study for 150 days. Based on measured food consumption (0.020−0.0235 kg/day) and body weights (0.243−0.271 kg) for the 150-day study, doses were approximately 330 (referent), 380 (normal K_2HPO_4), 1,100 (high K_2HPO_4), 400 (normal $[NaPO_3]_6$), or 1,100 (high $[NaPO_3]_6$) mg P/kg-day. At sacrifice, the same hematological and clinical chemistry parameters were evaluated (and including RBC count); organ weights (of the liver, heart, kidneys, spleen, and testes) were recorded. All animals were subjected to histopathological examinations (of the heart and kidneys). The right and left femur were measured (length); femurs and carcasses were analyzed for Ca and P content.

[10]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, 2011b), the LOAEL was converted by the U.S. EPA to an HED of 200 mg/kg-day using a DAF of 0.24 (HED = LOAEL × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$). Quantitative body-weight data for rats (0.232 kg) and reference body weights for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

Differences between the referent group and the normal ortho- and metaphosphate groups were noted by the study authors (nonsignificantly increased kidney weight in the "normal" phosphate groups), despite similar P doses (320, 380, and 400 mg P/kg-day, respectively) (Dymsza et al., 1959). Because the referent and normal K_2HPO_4 groups both received K_2HPO_4 at the same concentration (0.87%), these differences may be attributable to other elements of the diets (mineral salts and corresponding mineral levels noted above) that varied. Thus, for the purposes of this assessment, effects in the high K_2HPO_4 and high $(NaPO_3)_6$ groups were compared with the normal K_2HPO_4 and $(NaPO_3)_6$ groups, respectively.

In the group sacrificed after 60 days, the study authors reported that no significant differences occurred between the normal and high phosphate groups with respect to body-weight gain, food or protein consumption or efficiency, or Hb levels. Although the high K_2HPO_4 group was exposed to a higher dose of P, serum P levels were lower (although not statistically significant) in this group (7.2 mg/100 mL) than in the normal K_2HPO_4 group (8.3 mg/100 mL). No explanation for this phenomenon was provided by the study authors.

After 150 days of treatment, total body-weight gain was significantly higher (12%) in the high K_2HPO_4 group compared with the normal K_2HPO_4 group (see Table B-10); differences between the normal and high $(NaPO_3)_6$ groups were not significant (Dymsza et al., 1959). Animals administered high K_2HPO_4 or $(NaPO_3)_6$ did not exhibit differences in food or protein consumption, femur length, ash or Ca percent (dry) of femur bone, Hb levels, or RBC counts, when compared by the study authors with the normal groups. As in the group exposed for only 60 days, serum P was significantly higher in the normal K_2HPO_4 group compared with the high K_2HPO_4 group (7.8 mg/100 mL in normal and 6.0 mg/100 mL in high); the study authors offered no explanation. There were no significant differences between normal and high phosphate groups with respect to relative weights of liver or spleen (Dymsza et al., 1959). However, study authors reported kidneys in high dose animals (orthophosphate or metaphosphate) were significantly heavier ($p = 0.05$) than control rats. Rats administered the high $(NaPO_3)_6$ dose (1,100 mg P/kg-day as metaphosphate) showed significantly increased (11% higher than referent group) relative testes weights compared with the normal $(NaPO_3)_6$ group (Dymsza et al., 1959); the toxicological significance of this effect is uncertain. A NOAEL of 1,100 mg P/kg-day is identified for this study. The NOAEL of 1,100 mg P/kg-day corresponds to a NOAEL (HED) of 270 mg P/kg-day.[11]

Reproductive and Developmental Studies

The majority of reproductive and developmental toxicity studies of sodium or potassium salts of inorganic phosphates are technical reports (including those commissioned by FDA) and unpublished studies (many with limited information published in secondary sources). One published study of reproductive or developmental effects in laboratory animals was identified in the literature searches: Hodge (1964). Both the published and unpublished studies/technical reports lack information on concurrent Ca intake, and in most cases, dietary P levels. Table 11 summarizes the available information.

[11]The NOAEL was converted to an HED of 270 mg/kg-day using a DAF of 0.25 (HED = NOAEL × DAF). The DAF was calculated as follows: DAF = $(BW_a^{1/4} \div BW_h^{1/4})$. Quantitative body-weight data for rats (0.271 kg) and the reference body weight for humans (70 kg) recommended by U.S. EPA (1988) were used to calculate the DAF.

Table 11. Summary of Unpublished Reproductive and Developmental Toxicity Studies of Na/K Salts of Inorganic Phosphates

Ingredient	Strain/Species/ Sex/Number	Mode and Duration	Doses (mg P/kg-d)	Results	Reference
Combined repeat dose and reproductive/developmental screening studies					
PA	Sprague Dawley rats, 13/sex/group	Gavage 42−54 d (2 wk before, during, and after mating in males; females continued through gestation to PND 4)	NR (referent), 39.5, 79, or 158	At 158 mg P/kg-d, two females died; GI distension was observed. Soft, mucosal stool and a dirty nose were observed in one male at 158 mg P/kg-d. No clinical signs were observed, no differences in body-weight gain or food efficiency, and no differences in hematology, urinalysis, or neurobehaviors. Female rats exhibited decreased absolute kidney weight at all doses and decreased relative uterine weight at 158 mg P/kg-d. OECD (2009) reported a 2-wk. duration for this study but characterized it as an OECD Test Guideline 422 study. ECHA (2008) and CIR Expert Panel (2016) both reported treatment durations consistent with this Test Guideline (as shown under "Duration") and are assumed to report the correct duration. No reproductive or developmental effects were observed, including mating, conception, parturition, fetal survival, and body weight.	CIR Expert Panel (2016); OECD (2009); ECHA (2008)
K_2HPO_4	Sprague Dawley rats, 16/sex/group	Gavage 42−54 d (2 wk before, during, and after mating in males; females continued through gestation to PND 4)	NR (referent) or 180	No effects were observed on mating, male reproductive organ weights, or histopathology in male or female parents (tissues examined were not specified). No effects were observed on the numbers of corpora lutea, implantations, loss rate, birth rate, survival rate, or sex ratio. Exposure was reported as 2 wk. premating, 2 wk. mating, and 2 wk. post mating for males or 4 d parturition for females: 42 d (males) and 42−54 d (females). ECHA (2005) reported number of animals as 22, whereas CIR reported 16 animals/group.	OECD (2006); ECHA (2005)
Developmental toxicity studies					
$Na_5P_3O_{10}$, anhydrous	Dutch belted rabbits, 17−21 F/group	Gavage GDs 6−18	NR (referent), 0.6, 2.9, 13.6, or 63.1	No maternal toxicity and no effects were observed on pregnancy, numbers of corpora lutea, implantations or resorptions, or fetal survival or fetal weight. No treatment-related abnormalities in soft or skeletal tissues were noted.	FDRL (1973a)
$Na_5P_3O_{10}$, anhydrous	CD-1 mice, 21−24 F/group	Gavage GDs 6−15	NR (referent), 0.6, 2.8, 13.1, or 60.1	No effects were observed on maternal survival, numbers of implantations, fetal survival, or numbers of soft tissue or skeletal abnormalities were reported. Dose assumed to be reported as $Na_5P_3O_{10}$.	CIR Expert Panel (2016); FASEB/LSRO (1975)

Table 11. Summary of Unpublished Reproductive and Developmental Toxicity Studies of Na/K Salts of Inorganic Phosphates

Ingredient	Strain/Species/ Sex/Number	Mode and Duration	Doses (mg P/kg-d)	Results	Reference
$Na_5P_3O_{10}$, anhydrous	Wistar rats, 19−23 F/group	Gavage GDs 6−15	NR (referent), 0.4, 2.0, 9.3, or 42.9	No effects on maternal survival, numbers of implantations, fetal survival, or numbers of soft tissue or skeletal abnormalities were reported. Dose assumed to be reported as $Na_5P_3O_{10}$.	CIR Expert Panel (2016); FASEB/LSRO (1975)
$Na_5P_3O_{10}$, anhydrous	Golden hamsters, 19−23 F/group	Gavage GDs 6−10	NR (referent), 0.4, 1.6, 7.6, or 35.6	No effects on maternal survival, numbers of implantations, fetal survival, or numbers of soft tissue or skeletal abnormalities were observed. Dose assumed to be reported as $Na_5P_3O_{10}$.	CIR Expert Panel (2016); FASEB/LSRO (1975)
$Na_2H_2P_2O_7$	Wistar rats, 21−24 F/group	Gavage GDs 6−15	0.5, 2.6, 12.0, or 47.2	No treatment-related maternal toxicity and no effects on pregnancy, numbers of implantations or resorptions, or fetal survival were observed. No treatment-related increases in abnormalities in soft or skeletal tissue.	FDRL (1973b)
$Na_2H_2P_2O_7$	CD-1 mice, 24−25 F/group	Gavage GDs 6−15	NR (referent), 0.9, 4.4, 20.2, or 93.5	There was no treatment-related maternal toxicity and no effects on pregnancy, numbers of implantations or resorptions, or fetal survival or weight. No treatment-related increases in abnormalities in soft or skeletal tissue were noted.	FDRL (1973b)
$Na_2H_2P_2O_7$	Golden hamsters, 22−24 F/group	Gavage GDs 6−10	0.5, 2.2, 10, or 46.3	No treatment-related maternal toxicity, and no effects on pregnancy, numbers of implantations or resorptions, or fetal survival were observed. No treatment-related increases in soft or skeletal tissue abnormalities were noted.	FDRL (1973b)
$Na_2H_2P_2O_7$	Dutch belted rabbits, 9−12 F/group	Gavage GDs 6−18	0.4, 1.7, 7.7, or 35.7	No treatment-related maternal toxicity and no effects on pregnancy, numbers of corpora lutea, implantations, or resorptions, or fetal survival. No test-related increases in abnormalities in soft or skeletal tissue.	FDRL (1973b)
$Na_4P_2O_7$, anhydrous	CD-1 mice, 24−25 F/group	Gavage GDs 6−15	NR (referent), 0.3, 1.4, 6.5, or 30.3	No treatment-related maternal toxicity and no effects on pregnancy, numbers of corpora lutea, implantations, or resorptions, or fetal survival. No treatment-related abnormalities in fetal skeletal or soft tissue were observed. One pup in the 1.4 mg/kg-d treatment group had a fused/split rib and one pup in the 6.5 mg/kg-d exhibited soft tissue exophthalmos and encephalomeningocele, but neither malformation occurred in the high-dose group.	FDRL (1974a)
$Na_4P_2O_7$, anhydrous	Wistar rats, 23−25 F/group	Gavage GDs 6−15	NR (referent), 0.3, 1.5, 6.9, or 32.1	No treatment-related maternal toxicity and no effects on pregnancy, numbers of corpora lutea, implantations, or resorptions, or fetal survival were observed. No treatment-related increases in soft tissue or skeletal abnormalities were noted.	FDRL (1974a)

Table 11. Summary of Unpublished Reproductive and Developmental Toxicity Studies of Na/K Salts of Inorganic Phosphates

Ingredient	Strain/Species/ Sex/Number	Mode and Duration	Doses (mg P/kg-d)	Results	Reference
$(NaPO_3)_6$	CD-1 mice, 19−21 F/group	Gavage GDs 6−15	1.1, 5.2, 24.3, or 112.4	No treatment-related maternal toxicity and no effects on pregnancies or numbers of corpora lutea or implantations were observed. An increased incidence of resorptions was observed at the lowest dose only. Incidences of dead fetuses were 1/215 and 1/219 in the negative and positive control groups (respectively) and 2/213, 3/235, 3/224, and 4/228 at increasing doses; the differences from control were not statistically significant. No changes in numbers of abnormalities in soft or skeletal tissue were noted.	FDRL (1974b)
$(NaPO_3)_6$	Wistar rats, 20−25 F/group	Gavage GDs 6−15	0.7, 3.4, 15.7, or 72.9	No treatment-related maternal toxicity; no effects on pregnancy, corpora lutea, implants or resorptions; no effects on litter parameters or fetal survival and no changes in number of abnormalities in soft or skeletal tissue were observed.	FDRL (1974b)
KH_2PO_4	CD-1 mice, 20−22 F/group	Gavage GDs 6−15	0.7, 3.4, 15.7, or 72.8	No treatment-related maternal toxicity; no effects on pregnancy, corpora lutea, implants or resorptions; and no effects on litter parameters or fetal survival were observed. No treatment related changes in soft or skeletal tissue abnormalities were noted.	FDRL (1975)
KH_2PO_4	Wistar rats, 21−28 F/group	Gavage GDs 6−15	0.6, 3.0, 13.8, or 64.2	No treatment-related maternal toxicity; no effects of pregnancy, corpora lutea, implantation or resorptions; and no effects on litter parameters or fetal survival or fetal weight were observed. No changes in abnormal fetal development of soft or skeletal tissue compared with the sham control.	FDRL (1975)

CIR = cosmetic ingredient review; F = female(s); GD = gestation day; GI = gastrointestinal; K_2HPO_4 = dipotassium phosphate; KH_2PO_4 = monopotassium phosphate; NR = not reported; OECD = Organisation for Economic Co-operation and Development; $(NaPO_3)_6$ = sodium hexametaphosphate; $Na_2H_2P_2O_7$ = sodium dihydrogen pyrophosphate; $Na_4P_2O_7$ = tetrasodium phosphate; $Na_5P_3O_{10}$ = sodium tripolyphosphate; PA = phosphoric acid; PND = postnatal day.

In a published paper, Hodge (1964) summarized the results of unpublished three-generation reproductive toxicity studies of $Na_5P_3O_{10}$, sodium trimetaphosphate ($Na_5P_3O_{10}$), and $(NaPO_3)_6$. The summaries lacked details of study design and results. Hodge (1964) reported that for each compound, a dietary concentration of 0.5% administered to male and female rats had no effect on fertility, litter size, growth or survival of offspring, or organ weights or histopathology in F_3 offspring. This concentration is roughly estimated to provide doses in the range of 100−200 mg P/kg-day for adult animals, depending on compound.

Two combined repeat-dose and reproductive/developmental toxicity screening studies were performed; available information on these studies is from secondary sources (ECHA, 2018; CIR Expert Panel, 2016; OECD, 2009, 2006), as the original reports were not available. Administration of K_2HPO_4 at a dose of 180 mg P/kg-day for 42−54 days did not affect reproductive or developmental endpoints (see Table 11). In a comparable study of PA, however, two females exposed to 158 mg P/kg-day died prematurely; in addition, this dose was associated with reduced absolute kidney weight and relative uterine weight in females. No reproductive or developmental effects were observed, and no treatment-related findings were noted in males apart from soft stool and dirty nose in one high-dose rat.

In developmental toxicity studies of rats and mice administered PA, K_2HPO_4, $Na_5P_3O_{10}$, sodium dihydrogen pyrophosphate ($Na_2H_2P_2O_7$), $Na_4P_2O_7$, $(NaPO_3)_6$, or KH_2PO_4 on gestation days (GDs) 6−15, no maternal toxicity, developmental toxicity, or teratogenicity was observed (OECD, 2009, 2006; FDRL, 1975, 1974a, b, 1973b). Similarly, in rabbits administered $Na_2H_2P_2O_7$ or $Na_5P_3O_{10}$ on GDs 6−18, and in hamsters administered $Na_2H_2P_2O_7$ or $Na_5P_3O_{10}$ on GDs 6−10, no maternal toxicity was observed, and neither developmental toxicity nor teratogenicity was observed (CIR Expert Panel, 2016; FASEB/LSRO, 1975; FDRL, 1973a, b).

Taken together, these data suggest the sodium or potassium salts of inorganic phosphates are unlikely to produce maternal, developmental, or teratogenic toxicity. However, the lack of information on concurrent Ca intake and (in several cases) dietary contribution to P intake limits the confidence in these findings.

2.2.2. Inhalation Exposures

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

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

Section 2.3.1 provides an overview of genotoxicity studies (see Table 12) of Na/K salts of inorganic phosphates, and Sections 2.3.2–2.3.4 provide summaries of other supporting studies of Na/K salts of inorganic phosphates, including studies that did not report levels of Ca or P in the referent group diet (see Table 13); foreign language studies (see Table 14); and studies in which the exposure duration was <28 days (see Table 15).

2.3.1. Genotoxicity

Tests for mutagenicity in *Salmonella typhimurium* or *Escherichia coli* were negative in the presence or absence of activation for PA, sodium phosphate salts (NaH_2PO_4, Na_2HPO_4, $Na_2H_2P_2O_7$, $Na_4P_2O_7$, and $[NaPO_3]_6$), and potassium phosphate salts (KH_2PO_4, K_2HPO_4, and potassium pyrophosphate [$K_4P_2O_7$]) (Table 12). NaH_2PO_4 also tested negative in the SOS chromotest (without activation) (Quillardet et al., 1982 and Olivier and Marzin, 1987 as cited in CIR Expert Panel, 2016). Tests for mutagenicity in *Saccharomyces cerevisiae* (strains D3 or D4) produced negative results using NaH_2PO_4, $Na_2H_2P_2O_7$, $Na_4P_2O_7$, $(NaPO_3)_6$, K_2HPO_4, and $K_4P_2O_7$ (FDA, 1975 and Weiner et al., 2001 as cited in CIR Expert Panel, 2016; Litton Bionetics, 1975b, c). No clastogenic effects were observed in Chinese hamster lung (CHL) cells or WI-38 human lung cells treated with PA, Na_2HPO_4, $Na_2H_2P_2O_7$, $Na_5P_3O_{10}$, or K_2HPO_4 (Ishidate et al., 1984 as cited in CIR Expert Panel, 2016; NIER, 2005 as cited in both OECD, 2009; and OECD, 2006; Litton Bionetics, 1975a). Deoxyribonucleic acid (DNA) damage was observed in human lymphocytes treated with PA in a comet assay (Yilmaz et al., 2014), the only positive result in the database.

In vivo genotoxicity assays were negative, including tests for dominant lethal mutations in rats and host-mediated mutation assays in mice (and evaluated in *S. typhimurium* and *S. cerevisiae*) for $Na_2H_2P_2O_7$ and $Na_5P_3O_{10}$ (FDA, 1975 (PB262651) as cited in CIR Expert Panel, 2016; Litton Bionetics, 1975a). No effect on the frequency of translocations was seen in mice treated for 7 weeks with $Na_2H_2P_2O_7$ (FDA, 1975 as cited in CIR Expert Panel, 2016). Chromosomal aberrations (CAs) were not significantly induced in the bone marrow of rats treated with $Na_5P_3O_{10}$ (Litton Bionetics, 1975a).

Table 12. Summary of Sodium or Potassium Salts of Inorganic Phosphates Genotoxicity

Endpoint	Substance	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies in prokaryotic organisms							
Mutation	PA	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 uvrA	Up to 5,000 µg/plate	–	–	OECD 471 Guideline study. Cytotoxicity was noted at 5,000 µg/plate in TA100 (+S9)	NIER (2008) as cited in OECD (2009)
Mutation	PA	*S. typhimurium* strains TA97, TA98, TA100, TA102, and TA1535	NR	–	–	pHs ranged from 4 to 9. This study was deemed not assignable (lacking sufficient experimental details) in OECD (2009).	Cipollaro et al. (1986) as cited in CIR Expert Panel (2016); and OECD (2009)
Mutation	PA	*S. typhimurium* strains TA97, TA98, TA100, and TA104	0, 0.5, 1, 2 µL/plate	–	–	An appropriate positive control group was not used. This study was deemed not reliable in OECD (2009).	Al-Ani and Al-Lami (1988) as cited in CIR Expert Panel (2016); and OECD (2009)
Mutation	NaH_2PO_4; anhydrous	*S. typhimurium* TA1535, TA1537, and TA1538	0, 0.625, 1.25, 2.5%	–	–	Plate tests conducted at 1.25%; suspension tests up to 2.5%.	Litton Bionetics (1975c)
Mutation	Na_2HPO_4	*S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537	Up to 100 mg/plate	–	–	No additional information was reported.	Ishidate et al. (1984) as cited in CIR Expert Panel (2016)
Mutation	Na_2HPO_4	*S. typhimurium* strains TA98, TA100, TA1535, and TA1537	Up to 10,000 µg/plate	–	–	No additional information was reported.	Haworth et al. (1983) as cited in CIR Expert Panel (2016)
Mutation	$Na_2H_2P_2O_7$	*S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537	Up to 10 mg/plate	–	–	No additional information was reported.	Ishidate et al. (1984) as cited in CIR Expert Panel (2016)
Mutation	$Na_2H_2P_2O_7$	*S. typhimurium* strains TA97, TA98, TA100, TA102, and TA1535	5% (w/v)	–	–	No additional information was reported.	FDA (1975) as cited in CIR Expert Panel (2016)
Mutation	$Na_4P_2O_7$	*S. typhimurium* strains TA1535, TA1537, and TA1538	0, 0.05, 0.1% (w/v)	–	–	Plate and suspension tests.	Litton Bionetics (1975b)

Table 12. Summary of Sodium or Potassium Salts of Inorganic Phosphates Genotoxicity

Endpoint	Substance	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	$Na_4P_2O_7$	*S. typhimurium* strains TA98, TA100, TA1535, and TA1537; *E. coli* strain WP2 uvrA	0, 301.25, 602.5, 1,205, 2,410, 4,820 µg/plate	–	–	Positive and negative controls responded appropriately.	Kim et al. (2010)
Mutation	$(NaPO_3)_6$	*S. typhimurium* strains TA1535, TA1537, and TA1538	0, 0.018, 0.035%	–	–	Plate and suspension tests.	Litton Bionetics (1975d)
Mutation	KH_2PO_4	*S. typhimurium* strains TA1535, TA1537, and TA1538	Up to 5% (w/v)	–	–	No additional information was reported.	FDA (1975) as cited in CIR Expert Panel (2016)
Mutation	K_2HPO_4	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Up to 5 µL/plate	–	–	No additional information was reported. This study was deemed not assignable (lacking sufficient experimental details) in OECD (2006).	Weiner et al. (2001) as cited in CIR Expert Panel (2016)
Mutation	K_2HPO_4	*S. typhimurium* strains TA97 and TA102	Up to 10,000 µg/plate	–	–	Positive and negative controls responded appropriately.	Fujita and Sasaki (1994) as cited in OECD (2006)
Mutation	$K_4P_2O_7$	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Up to 5 µL/plate	–	–	No additional information was reported.	Weiner et al. (2001) as cited in CIR Expert Panel (2016)
DNA damage (SOS chromotest)	NaH_2PO_4	*E. coli* WP2 uvrA	10−100,000 nM/mL	–	NDr	No additional information was reported.	Quillardet et al. (1982) and Olivier and Marzin (1987) as cited in CIR Expert Panel (2016)
Genotoxicity studies in nonmammalian eukaryotic organisms							
Mutation	NaH_2PO_4; anhydrous	*Saccharomyces cerevisiae* strain D4	0, 2.5, 5, 10%	–	–	Suspension tests.	Litton Bionetics (1975c)
Mutation	$Na_2H_2P_2O_7$	*S. cerevisiae* (strain not specified)	NR	–	–	No additional information was reported.	FDA (1975) as cited in CIR Expert Panel (2016)

Table 12. Summary of Sodium or Potassium Salts of Inorganic Phosphates Genotoxicity

Endpoint	Substance	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Mutation	$Na_4P_2O_7$	*S. cerevisiae* strain D4	0, 1,13, 2.25% (w/v)	–	–	Suspension tests.	Litton Bionetics (1975b)
Mutation	$(NaPO_3)_6$	*S. cerevisiae* strain D4	0, 2.5, 5%	–	–	Suspension tests.	Litton Bionetics (1975d)
Mutation	K_2HPO_4	*S. cerevisiae* strain D4	Up to 5 µL/plate	–	–	No additional information was reported. This study was deemed not assignable (lacking sufficient experimental details) in OECD (2006).	Weiner et al. (2001) as cited in CIR Expert Panel (2016)
Mutation	$K_4P_2O_7$	*S. cerevisiae* strain D4	Up to 5 µL/plate	–	–	No additional information was reported.	Weiner et al. (2001) as cited in CIR Expert Panel (2016)
Genotoxicity studies in mammalian cells—in vitro							
CA	PA	CHL cells	0, 112.5, 225, 450 µg/mL	–	–	OECD 473 Guideline study.	NIER (2005) as cited in OECD (2009)
CA	Na_2HPO_4	CHL fibroblasts	Up to 2 mg/mL	–	NDr	No additional information was reported.	Ishidate et al. (1984) as cited in CIR Expert Panel (2016)
CA	$Na_2H_2P_2O_7$	CHL fibroblasts	Up to 0.5 mg/mL	–	NDr	No additional information was reported.	Ishidate et al. (1984) as cited in CIR Expert Panel (2016)
CA	$Na_5P_3O_{10}$	WI-38 human lung cells	0, 0.1, 1.0, 10 µg/mL	–	NDr	100 anaphase cells per dose were evaluated.	Litton Bionetics (1975a)
CA	K_2HPO_4	CHL cells	0, 1,250, 2,500, 5,000 µg/mL	–	–	OECD 473 Guideline study.	NIER (2005) as cited in OECD (2006)
DNA damage (comet assay)	PA	Human lymphocytes	0, 25, 50, 100, 200 µg/mL	+	NDr	Mean tail intensity and length significantly increased at all test concentrations. Cell viability >95%.	Yilmaz et al. (2014)

Table 12. Summary of Sodium or Potassium Salts of Inorganic Phosphates Genotoxicity

Endpoint	Substance	Test System	Doses/ Concentrations Tested[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies—in vivo							
Dominant lethal mutations	$Na_2H_2P_2O_7$	Rats (exposure NR)	Up to 720 mg/kg	−	NA	No additional information was reported.	FDA (1975) as cited in CIR Expert Panel (2016)
Dominant lethal mutations	$Na_5P_3O_{10}$	Male rats were exposed via gavage for 1 d (acute) or 5 d (subacute) and mated to unexposed females	0, 1,100 (subacute), or 2,500 mg/kg (acute)	−	NDr	Increased numbers of resorbed implants (acute study) or decreased fertility (subacute study) were noted.	Litton Bionetics (1975a)
Mutation (host-mediated assay)	$Na_2H_2P_2O_7$	Mice (exposure NR)	Up to 1,400 mg/kg	−	NDr	Responses evaluated *in S. typhimurium* strain TA1530 and *S. cerevisiae* strain D3.	FDA (1975) as cited in CIR Expert Panel (2016)
CA (heritable translocation assay)	$Na_2H_2P_2O_7$	Male mice were exposed in the diet for 7 wk at two dose levels	Up to 1,400 mg/kg	−	NA	No additional information was reported.	FDA (1975) as cited in CIR Expert Panel (2016)
CA (bone marrow)	$Na_5P_3O_{10}$	Male rats were exposed via gavage for 1 d (acute) or 5 d (subacute)	0, 1,100 (subacute), or 2,500 mg/kg (acute)	−	NDr	No significant induction of CAs at 1 or 5 d was noted.	Litton Bionetics (1975a)

CA = chromosomal aberration; DNA = deoxyribonucleic acid; K_2HPO_4 = dipotassium phosphate; $K_4P_2O_7$ = potassium pyrophosphate; KH_2PO_4 = monopotassium phosphate; $(NaPO_3)_6$ = sodium hexametaphosphate; NA = not applicable; $Na_2H_2P_2O_7$ = sodium dihydrogen pyrophosphate; Na_2HPO_4 = disodium phosphate; $Na_4P_2O_7$ = tetrasodium phosphate; $Na_5P_3O_{10}$ = sodium tripolyphosphate; NaH_2PO_4 = monosodium phosphate; NDr = not determined; OECD = Organisation for Economic Co-operation and Development; PA = phosphoric acid.

2.3.2. Supporting Animal Studies

Studies That Do Not Report Basal P and Ca Levels

Studies that did not provide information regarding P or Ca levels in the basal diet are summarized (by study type) in Table 13. Because these studies did not report the amount of P in the diet, dose estimates could not be calculated.

The most prominent effects identified in these studies pertain to the kidneys. In rats and dogs administered inorganic phosphates (as PA, NaH_2PO_4, Na_2HPO_4, trisodium phosphate [Na_3PO_4], $Na_4P_2O_7$, $Na_5P_3O_{10}$, $Na_5P_3O_{10}$, $[NaPO_3]_6$, and K_2HPO_4), increased kidney weights and histopathological evidence of kidney damage (including nephrocalcinosis, tubular damage, degeneration, and necrosis) were observed (Seo et al., 2011a; Pelham et al., 2009; Shibata et al., 1993; Schneider et al., 1981; Hodge, 1964; MacKay and Oliver, 1935). Decreased body weights (Pelham et al., 2009; Hodge, 1964) and effects on bone (decreased femur length and pathological effects) (Hodge, 1964) were also observed in rats administered inorganic phosphates. No effects on fertility or development in rats administered inorganic phosphates as $Na_5P_3O_{10}$, $Na_5P_3O_{10}$, or $(NaPO_3)_6$ were observed for three generations (Hodge, 1964).

Table 13. Supporting Studies: ≥28-Day Exposure but without Basal Intake of P or Ca

Strain/Species/ Sex/Number	Mode/ Duration	Dose or Dietary Concentration[a]	Results	Reference (notes)
Short-term (≥28 d) and subchronic studies				
Crl:CD (SD) rats; 10/sex/group	Gavage, 28 d	NR (control) or 5,130 mg/kg-d NaH_2PO_4 and Na_2HPO_4 in Fleet Phospho-Soda (not clear if mg Fleet or mg P)	Significant mortality occurred (eight males and seven females) starting in Week 2. Clinical signs of toxicity included dermal atonia, hypoactivity, impaired equilibrium, tremors, decreased respiration, and diarrhea. Food consumption and body weights were significantly decreased at 0−3 wk; surviving animals weighed 17% less than referents on Day 27. Absolute (but not relative) thymus weights were decreased. Histopathological effects in treated rats (surviving and dead) were nephrocalcinosis and tubular degeneration (kidney), mineralization (aorta and stomach), and degeneration and necrosis (heart and liver).	Pelham et al. (2009)
Sprague Dawley rats, 10/sex/group	Gavage, 5 d/wk for 90 d	0, 250, 500, or 1,000 mg $Na_4P_2O_7$/kg-d	No treatment-related mortality occurred. Increased WBC count (both sexes) and decreased RBC count (males only) were noted at 1,000 mg $Na_4P_2O_7$/kg-d. Liver weights were significantly increased at ≥500 mg $Na_4P_2O_7$/kg-d. Kidney lesions were reported at 1,000 mg $Na_4P_2O_7$/kg-d.	Seo et al. (2011a)
Albino rats, 18−25 F/group	Diet, 44 d	0 or 2.94% PA, 5.50% NaH_2PO_4, 6.53% Na_2HPO_4 or 4.92% in diet	Rats administered Na_2HPO_4 showed decreased final body weights relative to referents. All groups of treated rats showed increased kidney weights; this effect was accompanied by pathological signs of kidney damage (disorganization of the outer stripe of the outer zone of the medulla, cystic dilatation or collapse of tubules, and cell infiltration in the cortex).	MacKay and Oliver (1935)
Rats (strain not specified), 5 M/group	Diet, 1 mo	0 or 5% PA 0, 0.2, 2, or 10% $Na_5P_3O_{10}$, or $(NaPO_3)_6$	Decreased growth was reported in rats treated at 10% $Na_5P_3O_{10}$ or $(NaPO_3)_6$ in the diet. Rats administered 10% as $(NaPO_3)_6$ showed pale, swollen kidneys. Relative kidney weights were increased in rats treated at 10% in the diet (as $Na_5P_3O_{10}$ or $[NaPO_3]_6$). Tubular necrosis was observed in rats treated at 5% as PA, and at 10% as $Na_5P_3O_{10}$, $Na_5P_3O_{10}$, or $(NaPO_3)_6$; this effect was especially apparent in $Na_5P_3O_{10}$- and $(NaPO_3)_6$-treated rats. Some rats administered 2% in the diet exhibited acute inflammatory changes of the renal pelvis or tubular lesions.	Hodge (1964)
Chronic studies				
F344 rats, 15 M/group	Diet, 32 wk	0 or 3% NaH_2PO_4 or Na_3PO_4	Body weights were not significantly affected by treatment. Changes in urinary pH and the urinary concentrations of P (increased) and Ca (decreased) were noted. Absolute (but not relative) bladder weights were increased in Na_3PO_4-treated rats; absolute kidney weights were increased in both dose groups. Na_3PO_4-treated rats showed significantly increased incidences of hyperplasia in the urinary bladder and calcification of the renal pelvis.	Shibata et al. (1993)
Beagle dogs, 5 M/group	Gavage, 22 wk	0 or 1,330 mg Na_2HPO_4/kg-d or 1,700 mg K_2HPO_4/kg-d (TWA)	One K_2HPO_4-treated dog died (Week 12); autopsy revealed enlarged, yellow kidneys and diffuse calcification. Vomiting was noted, especially during the first week of treatment. Nephrocalcinosis and disseminated atrophy of the proximal tubule were reported. Kidney effects were confined to the cortex in Na_2HPO_4-treated rats; however, lesions were observed in both the cortex and medulla of K_2HPO_4-treated rats.	Schneider et al. (1981)

Table 13. Supporting Studies: ≥28-Day Exposure but without Basal Intake of P or Ca

Strain/Species/ Sex/Number	Mode/ Duration	Dose or Dietary Concentration[a]	Results	Reference (notes)
Rochester rats, 50/sex/group	Diet, 2 yr	0, 0.05, 0.5, or 5% $Na_5P_3O_{10}$ or $(NaPO_3)_6$; 0, 0.1, 1.0, or 10% $Na_5P_3O_{10}$	The incidence of mortality was high; however, deaths were most frequently attributed to respiratory infection or pericarditis/peritonitis. Decreased body weights were reported at 5 and 10% in the diet as $Na_5P_3O_{10}$ or $(NaPO_3)_6$. Kidney weights were increased in rats at 5% $Na_5P_3O_{10}$; femur length was decreased. In general, analyses of these parameters were confounded by infection or reductions in growth. Histopathological examinations revealed changes consistent with chronic tubular nephropathy (5% as $Na_5P_3O_{10}$) and calcification in the tubules of the kidneys (5% as $[NaPO_3]_6$). No evidence of carcinogenicity was observed.	Hodge (1964)
Reproductive and developmental studies				
Rats (strain not specified), 16 F and 8 M/group	Diet, 3 generations	0 or 0.5% $Na_5P_3O_{10}$, $(NaPO_3)_3$, or $(NaPO_3)_6$	No significant, treatment-related effects on fertility, litter size, or the survival and growth of offspring were observed. Third-generation rats (sacrificed at 100 d of age) showed no changes in organ weights or gross or microscopic pathology.	Hodge (1964)

[a]Because these studies did not report P content of the baseline diet/control group, doses in terms of mg P/kg-day were not calculated.

Ca = calcium; K_2HPO_4 = dipotassium phosphate; KH_2PO_4 = monopotassium phosphate; F = female(s); M = male(s); $(NaPO_3)_3$ = sodium trimetaphosphate; $(NaPO_3)_6$ = sodium hexametaphosphate; Na_2HPO_4 = disodium phosphate; Na_3PO_4 = trisodium phosphate; $Na_4P_2O_7$ = tetrasodium phosphate; $Na_5P_3O_{10}$ = sodium tripolyphosphate; NaH_2PO_4 = monosodium phosphate; NR = not reported; P = phosphorus; PA = phosphoric acid; RBC = red blood cell; TWA = time-weighted average; WBC = white blood cell.

Foreign Language Studies

Information about foreign language studies (Table 14) was obtained mainly from secondary sources (CIR Expert Panel, 2016; WHO, 1982). These studies identify the kidney as a primary target of toxicity following exposure to inorganic phosphates (NaH_2PO_4, Na_2HPO_4, $Na_4P_2O_7$, $Na_5P_3O_{10}$, $[NaPO_3]_n$, K_2HPO_4, and $K_4P_2O_7$) (Shimoji et al., 1988; Schneider et al., 1980a, 1980b; Hahn, 1961; Hahn and Seifen, 1959; Hahn et al., 1958; Hahn et al., 1956; Nishii, 1993 all as cited in CIR Expert Panel, 2016; or WHO, 1982). The most common renal effects identified included increased weight and evidence of calcification (Shimoji et al., 1988; Schneider et al., 1980a, 1980b; Hahn, 1961; Hahn and Seifen, 1959; Hahn et al., 1958; Hahn et al., 1956; Nishii, 1993 all as cited in CIR Expert Panel, 2016; or WHO, 1982); less common effects were renal failure (Shimoji et al., 1988 as cited in CIR Expert Panel, 2016), nephropathy (Nishii et al., 1993 as cited in CIR Expert Panel, 2016), tubular atrophy (Schneider et al., 1980b, 1980a as cited in CIR Expert Panel, 2016), or necrosis (Shimoji et al., 1988 as cited in CIR Expert Panel, 2016). Owing to the limited information available in the secondary sources, the basal level of phosphate in the diet (i.e., phosphate exposure in the referent group), and the units of the reported concentrations (percent compound or percent P in diet), was generally not known; thus, doses were not estimated for this review.

Table 14. Supporting Studies Published in Foreign Languages with English Summary Available

Strain/Species/ Sex/Number	Mode/ Duration	Dietary Concentrations[a] (as reported in secondary source)	Results	Reference
Rats (strain and sex not specified), 34−36/group	Diet, 24 wk	0, 1.8, 3, or 5% NaH_2PO_4, Na_2HPO_4, $Na_4P_2O_7$, or $Na_5P_3O_{10}$ ($Na_5P_3O_{10}$ tested at pH 5 and 9.5)	A slight but significant increase in kidney weight was reported at 1.8% NaH_2PO_4. Rats treated at 3 and 5% NaH_2PO_4 showed evidence of kidney damage (i.e., nephrocalcinosis). A slight but statistically significant increase in kidney weight was reported in rats treated at 1.8% Na_2HPO_4 in the diet. Rats treated at 3 and 5% Na_2HPO_4 showed a significant reduction in growth and evidence of kidney damage (i.e., nephrocalcinosis). With $Na_5P_3O_{10}$ and $Na_4P_2O_7$ growth was adversely affected at 5%. $Na_5P_3O_{10}$ induced nephrocalcinosis at 3 and 5%, while calcification was slight or absent and kidney weights were unaffected at 1.8%. Nephrocalcinosis was reported at all doses of $Na_5P_3O_{10}$; damage was less prevalent at pH 5 than at pH 9.5.	Hahn and Seifen (1959) as cited in CIR Expert Panel (2016); or WHO (1982)
Rats (number, strain, and sex not specified)	Diet, 39 wk	0 or 1.1% NaH_2PO_4; 0, 1.1, 1.8, 3, or 5% Na_2HPO_4, $Na_4P_2O_7$, or $Na_5P_3O_{10}$	Slight kidney calcification was reported in rats treated at 1.1% NaH_2PO_4 or Na_2HPO_4. Effects of $Na_4P_2O_7$ and $Na_5P_3O_{10}$ were not reported. According to CIR Expert Panel (2016), the LOEL was 495 mg/kg-d (based on food consumption and body weight values of 0.018 kg/d and 0.35 kg, respectively); whether the dose was as P or as the compound was unclear.	Hahn and Seifen (1959) as cited in CIR Expert Panel (2016); or WHO (1982)
Male Wistar rats (number not specified)	Diet, 8 wk	0 or 10% K_2HPO_4	Kidney toxicity was reported in rats treated at 10% in the diet.	Nishii et al. (1993) as cited in CIR Expert Panel (2016)
	Diet (duration not specified)	0 or 5% K_2HPO_4	Renal calcification and severe nephropathy were reported.	
Beagle dogs, *n* = 15	Diet, 14 or 38 wk	0 or 800 mg/kg-d as K_2HPO_4 (not clear if mg K_2HPO_4 or mg P)	Evidence of kidney damage was found in all dogs (severity was greater at 38 wk compared with 14 wk). Renal damage included disseminated tubular atrophy (predominantly affecting the proximal tubules), focal scar tissue, and nephrocalcinosis.	Schneider et al. (1980a,1980b) as cited in CIR Expert Panel (2016)
F344 rats, 60/sex/group	Diet (duration not specified)	0.6, 1.25, 2.5, 5, or 10% as $K_4P_2O_7$; whether the 0.6%-group was the study control was unclear	Three rats treated at 10% in the diet died; deaths were attributed to renal failure. Histopathological effects noted at 2.5 and 5% included necrosis and calcification of renal tubules, ulceration or granuloma formation in the tongue mucosa, and hypertrophy of the salivary glands.	Shimoji et al. (1988) as cited in CIR Expert Panel (2016)

[a]CIR Expert Panel (2016) did not clearly indicate whether the dietary concentrations were reported as percent compound or percent P in diet. For the purpose of this table, the percentages were assumed to be as the compound. In addition, because the CIR Expert Panel (2016) did not report P content of the baseline diet/control group, doses in terms of mg P/kg-day were not calculated.

$K_4P_2O_7$ = potassium pyrophosphate; KH_2PO_4 = monopotassium phosphate; LOEL = lowest-observed-effect level; Na_2HPO_4 = disodium phosphate; $Na_4P_2O_7$ = tetrasodium phosphate; $Na_5P_3O_{10}$ = sodium tripolyphosphate; NaH_2PO_4 = monosodium phosphate.

Short-Term Studies

Short-term studies (typically 14−28 days in duration) are summarized in Table 15. The following types of effects were identified in these studies:

- **Decreased growth.** Rats administered diets containing NaH_2PO_4, $Na_5P_3O_{10}$, KH_2PO_4, or potassium tripolyphosphate ($K_5P_3O_{10}$) at ≥960 mg P/kg-day showed decreased body weights relative to referents (Katsumata et al., 2015; Katsumata et al., 2005; Matsuzaki et al., 2002; Matsuzaki et al., 1999).
- **Changes in serum chemistry associated with kidney function.** Rats treated with phosphates at ≥960 mg P/kg-day as NaH_2PO_4 or $K_5P_3O_{10}$ showed significantly increased BUN (Matsuzaki et al., 1999; Matsuzaki et al., 1997).
- **Increased kidney weights.** In most studies, rats treated with phosphates in the diet as NaH_2PO_4, $Na_5P_3O_{10}$, KH_2PO_4, or $K_5P_3O_{10}$ showed significantly increased kidney weights. Effects were seen at approximately ≥1,000 mg P/kg-day (Katsumata et al., 2015; Matsuzaki et al., 2010; Matsuzaki et al., 2002; Matsuzaki et al., 1999).
- **Evidence of kidney damage.** Increased kidney weights were accompanied by kidney lesions, most frequently, nephrocalcinosis (Katsumata et al., 2015; Matsuzaki et al., 2010; Matsuzaki et al., 2002; Matsuzaki et al., 1999). In one study (Matsuzaki et al., 1997), changes to the proximal tubules (vacuoles, lysosomes, swelling of microvilli, hydroxyapatite deposits) were noted in rats treated at 1,400 mg P/kg-day as $K_5P_3O_{10}$.
- **Bone effects.** Two studies by Katsumata et al. (2015) and Koshihara et al. (2005) showed increased markers of bone turnover, decreased compression or bending load, and decreased bmc or bmd (femur, tibia, or lumbar vertebra) in rats administered ≥830 mg P/kg-day as KH_2PO_4.

Table 15. Supporting Studies of Acute or Short-Term (<28 Days) Exposure Duration

Strain/Species/ Sex/Number	Mode/ Duration	Dietary P Concentration (%)	Dietary Ca Concentration (%)	Results	Reference
Wistar rats, 5 males/group	Diet, 21 d	0.3 (referent) or 1.4% (as NaH_2PO_4, calculated for this review)	0.5% (both groups)	Rats treated at 1.4% in the diet showed significantly decreased food consumption and body weights (23% lower than referents). Serum BUN was significantly increased. Kidney concentrations of P and Ca and relative kidney weights were also significantly increased. All animals showed evidence of nephrocalcinosis (mean severity score = 1.6; maximum score = 4). Based on measured food consumption (0.0178 and 0.0131 kg/d) and body weights (0.207 and 0.173 kg), 0.3 and 1.4% in the diet are equivalent to approximately 260 and 1,100 mg P/kg-d.	Matsuzaki et al. (1999)
Wistar rats, 5 males/group	Diet, 21 d	0.3 (referent) or 1.4% (as $Na_5P_3O_{10}$, calculated for this review)	0.5% (both groups)	Rats treated at 1.4% in the diet showed significantly decreased food consumption and body weights (35% lower than referents). Urinary albumin and NAG activity were significantly increased. Kidney concentrations of P and Ca and relative kidney weights were also significantly increased. All animals showed evidence of nephrocalcinosis (mean severity score = 3.8; maximum score = 4). Based on measured food consumption (0.0183 and 0.0108 kg/d) and body weights (0.206 and 0.157 kg), 0.3 and 1.4% in the diet are equivalent to approximately 270 and 960 mg P/kg-d.	Matsuzaki et al. (1999)
Wistar rats, 5 males/group	Diet, 14 d	0.3 (referent) or 1.2% (as KH_2PO_4)	0.5% (both groups)	Food consumption and body weights were not significantly affected by treatment. Rats treated at 1.2% in the diet showed significantly decreased levels of magnesium and Ca and significantly increased levels of P, PTH, osteocalcin, and C-terminal telopeptide of type I collagen (CTx) in the serum. No significant effects were observed on femoral mineral content (with respect to P, Ca, or magnesium). Based on measured food consumption (0.0219 and 0.0210 kg/d) and body weights (0.169 and 0.162 kg), 0.3 and 1.2% in the diet are equivalent to approximately 390 and 1,600 mg P/kg-d.	Matsuzaki et al. (2010)

Table 15. Supporting Studies of Acute or Short-Term (<28 Days) Exposure Duration

Strain/Species/ Sex/Number	Mode/ Duration	Dietary P Concentration (%)	Dietary Ca Concentration (%)	Results	Reference
Wistar rats, 6 males/group	Diet, 21 d	0.3 (referent), 0.9, or 1.5% (as KH_2PO_4)	0.5% (both groups)	Food consumption and body weights were statistically significantly decreased at 1.5% in the diet. Relative to referents, rats treated at 0.9 and 1.5% in the diet showed significant increases in serum P, excretion of CTx (a marker of bone turnover), bone formation rate (lumbar vertebra), osteoclast number (tibia and lumbar vertebra), and mRNA expression of receptor activator of NF-kB ligand (RANKL; femur); bmc and bmd (femur and lumbar vertebra) and ultimate compression load (lumbar vertebra) were significantly decreased. Additional effects at 1.5% in the diet included significantly decreased serum Ca, increased serum PTH and osteocalcin, and decreased ultimate bending load (femur). Based on measured food consumption (0.017, 0.017, and 0.012 kg/d) and body weights (0.187, 0.184, and 0.154 kg), 0.3, 0.9, and 1.5% in the diet are equivalent to approximately 270, 830, and 1,200 mg P/kg-d.	Katsumata et al. (2005)
Wistar rats, 6 males/group	Diet, 21 d	0.3 (referent) or 1.5% (as KH_2PO_4)	0.5% (both groups)	Food consumption and body weights were statistically significantly decreased at 1.5% in the diet. Relative to referents, rats treated at 1.5% in the diet showed significantly decreased serum Ca and increased serum P, PTH, and osteocalcin; increased urinary albumin, CTx, NAG activity, and β2-microglobulin excretion; increased kidney Ca and P and increased relative kidney weight; decreased bmc and bmd (femur, tibia, and lumbar); and increased RANKL expression (femur). Based on measured food consumption (0.017 and 0.014 kg/d) and body weights (0.195 and 0.172 kg), 0.3 and 1.5% in the diet are equivalent to approximately 260 and 1,200 mg P/kg-d.	Katsumata et al. (2015)
Wistar rats, 5 males/group	Diet, 21 d	0.3 (referent) or 1.4% (as KH_2PO_4, calculated for this review)	0.5% (both groups)	Rats treated at 1.4% in the diet showed significantly decreased food consumption and body weights (21% lower than referents). Serum BUN was significantly increased. Relative kidney weights were also statistically significantly increased. All animals showed evidence of nephrocalcinosis (mean severity score = 1.2; maximum score = 4). Based on measured food consumption (0.0177 and 0.0143 kg/d) and body weights (0.202 and 0.173 kg), 0.3 and 1.4% in the diet are equivalent to approximately 260 and 1,200 mg P/kg-d.	Matsuzaki et al. (1999)

Table 15. Supporting Studies of Acute or Short-Term (<28 Days) Exposure Duration					
Strain/Species/ Sex/Number	**Mode/ Duration**	**Dietary P Concentration (%)**	**Dietary Ca Concentration (%)**	**Results**	**Reference**
Wistar rats, 5/sex/group	Diet, 21 d	0.3 (referent), 0.6, 0.9, 1.2, or 1.5% (as KH_2PO_4)	NR	Food consumption and body weights were adversely affected in rats treated at 1.5% in the diet. Creatinine clearance was higher in rats of both sexes treated at 1.5% in the diet; urinary albumin was significantly increased at ≥0.9% in both sexes. Kidney concentrations of Ca and P were significantly increased in males at 1.2 or 1.5%, and in all groups of treated females. Relative kidney weights were statistically significantly increased in 1.5% males and 1.2 and 1.5% females. Based on measured food consumption (0.018−0.021 kg/d in males and 0.014−0.017 kg/d in females) and body weights (0.197−0.224 kg in males and 0.156−0.177 kg in females), 0.3, 0.6, 0.9, 1.2, and 1.5% in the diet are equivalent to approximately 280, 550, 820, 1,100, and 1,400 mg P/kg-d in males and 290, 560, 860, 1,100, and 1,400 mg P/kg-d in females.	Matsuzaki et al. (2002)
Wistar rats, 42 males/group	Diet, 21 d (sacrificed at 0, 1, 3, 5, 7, 14, and 21 d)	0.5 (referent) or 1.5% (as $K_5P_3O_{10}$)	0.5% (both groups)	Rats treated at 1.5% in the diet showed significantly increased serum BUN (21 d), decreased urinary pH (21 d), and increased urinary albumin (3−21 d), NAG activity (1−21 d), and β2-microglobulin excretion (14−21 d). After 21 d, kidney concentrations of P and Ca and kidney weights were statistically significantly increased. Nephrocalcinosis was noted in 4/6 rats after 1 d and in 6/6 rats at all other time points; the severity of kidney effects increased over time. Changes in the proximal tubules included vacuoles, lysosomes, and swelling of the microvilli (1 d); giant lysosomes with Ca deposits and hydroxyapatite deposition in mitochondria (3 d); hydroxyapatite deposition in microvilli (5 d); and necrotic cells (21 d). Based on reference values for food consumption (0.0204 kg/d) and body weights (0.217 kg) for male Wistar rats, 0.5 and 1.5% in the diet are equivalent to approximately 470 and 1,400 mg P/kg-d.	Matsuzaki et al. (1997)

Table 15. Supporting Studies of Acute or Short-Term (<28 Days) Exposure Duration

Strain/Species/ Sex/Number	Mode/ Duration	Dietary P Concentration (%)	Dietary Ca Concentration (%)	Results	Reference
Wistar rats, 5 males/group	Diet, 21 d	0.3 (referent) or 1.4% (as $K_5P_3O_{10}$, calculated for this review)	0.5% (both groups)	Rats treated at 1.4% in the diet showed significantly decreased food consumption and body weights (43% lower than referents). Serum BUN and urinary albumin and NAG activity were significantly increased. Kidney concentrations of P and Ca and relative kidney weights were also significantly increased. All animals showed evidence of nephrocalcinosis (mean severity score = 3.2; maximum score = 4). Based on measured food consumption (0.0189 and 0.0101 kg/d) and body weights (0.208 and 0.146 kg), 0.3 and 1.4% in the diet are equivalent to approximately 270 and 970 mg P/kg-d.	Matsuzaki et al. (1999)

bmc = bone mineral content; bmd = bone mineral density; BUN = blood urea nitrogen; Ca = calcium; $K_5P_3O_{10}$ = potassium tripolyphosphate; KH_2PO_4 = monopotassium phosphate; mRNA = messenger RNA; NAG = N-acetyl-β-D-glucosaminidase; $Na_5P_3O_{10}$ = sodium tripolyphosphate; NaH_2PO_4 = monosodium phosphate; NR = not reported; P = phosphorus; PTH = parathyroid hormone.

2.3.3. Metabolism/Toxicokinetics

Inorganic phosphate is absorbed from the GI tract, with net P absorption ranging from 55 to 80% of intake in adults and from 60 to 95% of intake in infants and children (EFSA, 2015; IOM, 1997). Intestinal absorption occurs by passive absorption at tight junctions between intestinal cells and by sodium-dependent active transport, with the relative contribution of each mechanism dependent on the luminal concentration of phosphate (Chang and Anderson, 2017; EFSA, 2015; Lee and Marks, 2015; Marks et al., 2010). Multiple sodium-dependent transporters are proposed to mediate intestinal phosphate absorption in rats, including the intestinal type II sodium phosphate cotransporter, NaPi-IIb, and Type III transporters, PiT1 and PiT2 (Candeal et al., 2017; Marks et al., 2010). NaPi-IIb plays a key role in intestinal absorption of inorganic phosphate at low dietary concentrations or during fasting; however, studies in NaPi-IIb knockout mice suggest the sodium-independent pathway is also important, especially when dietary phosphate levels are elevated (Chang and Anderson, 2017; Lee and Marks, 2015). Intestinal phosphate absorption by active transport is physiologically regulated by dietary phosphate, PTH, 1,25-dihydroxy-vitamin D_3, epidermal growth factor, glucocorticoids, estrogen, metabolic acidosis, and phosphatonins including FGF-23 (EFSA, 2015; Lee and Marks, 2015).

The oral bioavailability of inorganic phosphates depends largely on the amount of coingested Ca, which can bind with high affinity to phosphate in the digestive tract and prevent its absorption (EFSA, 2015). A study of Ca and P balance in healthy adults revealed increased dietary Ca intake without a corresponding increase in phosphate intake reduced the absorption of phosphate from the intestine (Heaney and Nordin, 2002). In dietary studies, oral bioavailability also depends on the food source (animal or plant derived) and the organic or inorganic form of the P-containing compound (EFSA, 2015; Calvo and Tucker, 2013). Organic forms of phosphate esters require enzymatic hydrolysis by phosphatases in the intestinal lumen to produce phosphate that can be absorbed (EFSA, 2015; Calvo and Tucker, 2013). This slows the phosphate absorption rate and reduces the efficiency of phosphate absorption from organic sources. In addition, humans lack the enzyme needed to digest phytic acid, which is the storage form of P in plants. Intestinal bacteria contain phytase, however, which can hydrolyze phytic acid and increase the bioavailability of phosphate from plant sources (EFSA, 2015). Food additives and supplements contain inorganic salts of phosphate, which dissociate readily in the gut and are rapidly absorbed and highly bioavailable (EFSA, 2015; Calvo and Tucker, 2013). Noori et al. (2010b) estimated the GI absorption of P to be 10−30% for plant-based proteins, compared with 40−60% from animal protein and 80−100% from additives and preservatives.

Phosphate ions (i.e., HPO_4^{2-} and $H_2PO_4^-$) are transported in blood plasma, with approximately 85−90% existing as free serum phosphate and 10−15% bound to protein (EFSA, 2015). Phosphorus is stored in bones and teeth, primarily as a hydroxyapatite complex with Ca (EFSA, 2015). Total body P in adults exists as approximately 85% hydroxyapatite, 14% as components of cells in soft tissues, and 1% in serum (Chang and Anderson, 2017). Phosphate is present in breast milk and crosses the placenta during pregnancy using sodium-dependent transporters (i.e., NaPi-IIb) and is maintained in fetal serum at higher concentrations than found in the maternal circulation (EFSA, 2015).

Inorganic phosphates are eliminated in both urine and feces (EFSA, 2015). Under normal dietary conditions, approximately 10−20% of the P filtered by the kidney is ultimately excreted, with the remainder being reabsorbed in the proximal tubule (Chang and Anderson, 2017; EFSA, 2015; Marks et al., 2010). Sodium-phosphate cotransporters, NaPi-IIa, NaPi-IIc and PiT2, are

responsible for the reabsorption of phosphate in renal tubules (Chang and Anderson, 2017; EFSA, 2015). Inorganic phosphates found in feces arise from pancreatic, biliary, and intestinal secretions (EFSA, 2015).

Serum phosphate levels are maintained within relatively narrow limits by interactions or crosstalk between the intestine, kidney, parathyroid glands, and bone (Chang and Anderson, 2017; Ritter and Slatopolsky, 2016; EFSA, 2015; Anderson, 2013). PTH and FGF-23 (produced by bone osteoblasts and osteocytes) reduce serum phosphate levels by downregulating the renal cotransporters NaPi-IIa and NaPi-IIc, resulting in decreased phosphate reabsorption and increased excretion by the kidney (Chang and Anderson, 2017; EFSA, 2015; Lee and Marks, 2015; Anderson, 2013; Marks et al., 2010). Increased serum phosphate concentrations also produce a reduction in renal 1,25-dihydroxy-vitamin D_3 synthesis, resulting in decreased intestinal absorption of phosphate (Brown and Razzaque, 2015; EFSA, 2015; Lee and Marks, 2015; Marks et al., 2010). Conversely, a reduction in serum phosphate levels decreases PTH and FGF-23 release, resulting in decreased renal excretion of P. 1,25-Dihydroxy-vitamin D_3 synthesis in the kidney also increases when serum phosphate is low, resulting in enhanced intestinal absorption of phosphate (EFSA, 2015). Klotho is a transmembrane protein that is necessary for FGF-23 receptor binding and signal transduction in the kidney and parathyroid glands. Experiments with Klotho knockout mice indicate that this protein is a critical cofactor in regulation of phosphate homeostasis by FGF-23 (Erben and Andrukhova, 2017; Ritter and Slatopolsky, 2016; Gutiérrez, 2013).

Serum phosphate concentrations are not considered a reliable biomarker for dietary exposure because these homeostatic mechanisms maintain serum phosphate levels within a narrow range, even in the presence of wide variations in intake (EFSA, 2015). Urinary phosphate excretion is similarly regulated by homeostatic mechanisms and thus has limitations as a potential biomarker for oral exposure (EFSA, 2015).

2.3.4. Mode-of-Action/Mechanistic Studies

Disruption of phosphate homeostasis leads to renal and cardiovascular toxicity and decreased bone health. Altered endocrine communication between bone-derived FGF-23 and kidney-derived α-Klotho leads to increased serum phosphate levels (Brown and Razzaque, 2015; Gutiérrez, 2013). α-Klotho changes cellular Ca homeostasis, by both increasing the expression and activity of TRPV5 (a Ca channel protein, decreasing phosphate reabsorption in the kidney) and decreasing that of TRPC6 (a receptor-activated Ca channel, decreasing phosphate absorption from the intestine). α-Klotho increases kidney Ca reabsorption by stabilizing TRPV5 (Huang, 2010). Mice lacking either FGF-23 or the α-Klotho enzyme display premature aging due to hyperphosphatemia. Many of these symptoms can be alleviated by feeding the mice a low-phosphate diet (Kuro, 2019). Elevated serum phosphate combines with free ionized serum Ca to form a Ca-P product that can be deposited in tissues in a process referred to as ectopic calcification (Brown and Razzaque, 2015). Ectopic calcification in the renal parenchyma leads to tubule damage and interstitial fibrosis (Chang and Anderson, 2017; Brown and Razzaque, 2015).

Ectopic calcification also occurs in vascular endothelial cells, leading to arteriosclerosis, hypertension, LVH, and aortic valve disease (Brown and Razzaque, 2015; Anderson, 2013). Increasing serum Ca-P product upregulates osteocalcin, a bone matrix protein, which promotes further vascular calcification (Brown and Razzaque, 2015). Studies in cultured vascular smooth muscle cells show that high phosphate concentrations promote expression of osteochondrogenic

differentiation markers and extracellular matrix calcification (Menon and Ix, 2013). Other mechanisms that may contribute to hypertension include impaired vasodilation in endothelial cells, high serum PTH levels, and increased renin-angiotensin activity (Brown and Razzaque, 2015; Anderson, 2013). Cardiovascular disease is commonly found in patients with hyperphosphatemia resulting from CKD (Chang and Anderson, 2017; Ritter and Slatopolsky, 2016; Nadkarni and Uribarri, 2014).

The Ca:P ratio in the diet influences bone health (Brown and Razzaque, 2015; EFSA, 2015). Experimental animal studies have demonstrated that a high P intake combined with a low Ca intake results in bone resorption, low peak bone mass, and increased bone fragility (EFSA, 2015; Calvo and Tucker, 2013). Cross-sectional studies in humans suggest an association between the dietary Ca:P molar ratio and bmd (EFSA, 2015; Calvo and Tucker, 2013). Calvo and Tucker (2013) suggested that phosphate-induced dysregulation of PTH, FGF-23, and 1,25-dihydroxy-vitamin D_3 may contribute to progressive bone loss with age (i.e., osteoporosis). Increased serum P also causes hyperplasia of the parathyroid gland, leading to secondary hyperparathyroidism, followed by high-turnover bone disease and increased risk of fracture (Nadkarni and Uribarri, 2014).

Little information is available on potential mechanisms of phosphate-induced cancer. A review by Brown and Razzaque (2018) hypothesizes that phosphate is a mitogenic factor that can enhance tumor cell growth, with excessive phosphate stimulating growth promoting cell signaling and neovascularization. Wilson et al. (2015) postulated a role for P-induced increases in PTH influencing the metastasis of prostate tumors to bone. These study authors noted that PTH promotes bone remodeling, and that prostate cancer is more likely to metastasize to bone when remodeling activity is higher. This sequence of events was suggested as a possible explanation for the shorter latency to prostate cancer diagnosis observed in their study (Wilson et al., 2015).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

The human and animal toxicity literature for dietary P and Na/K salts of inorganic phosphates, coupled with mechanistic information, clearly indicates that impaired P homeostasis is associated with renal toxicity (acute phosphate nephropathy/nephrocalcinosis) and GI symptoms, is potentially associated with cardiovascular effects (including increased risk of mortality or cardiovascular events), and may alter bone composition.

As discussed earlier, oral data pertinent to the hazard assessment of sodium or potassium salts of inorganic phosphates can be grouped into four main categories: human epidemiological studies on associations between dietary P intake and health outcomes; controlled trials of humans exposed to sodium or potassium salts of inorganic phosphates for acute or short-term durations; human studies of renal toxicity or GI symptoms after acute exposure to OSP for bowel cleansing or constipation treatment; and short-term and subchronic animal toxicity studies. Sections 2.1 and 2.2 above provide the rationales for selecting human and animal data for consideration in the assessment, and these details will not be reiterated here.

All the above sources were considered relevant to hazard assessment. However, several of these sources suffer from limitations that render them less useful for dose-response assessment. Specifically, the human dietary intake studies have uncertainties that preclude their use for dose-response assessment. These include potential underestimation of dose estimates and varying bioavailabilities of different P sources. In addition, although the acute colonoscopy preparation studies provide important hazard information and identify clear effect levels, the considerable uncertainty involved in extrapolating from a single-day exposure to subchronic or chronic exposure limits value of these data for dose-response assessment.

Dietary intake of phosphates is difficult to quantify. EFSA (2015) noted that food product processing and formulations change continuously, making it difficult for food composition databases to keep pace with the changes. Further, P-containing food additives are used in a large variety of foods including baked goods, meats, and beverages. To capture the inputs from all of these sources for an epidemiological study requires that the FFQ include all of these foods and be updated over time to reflect changing content. Whether an FFQ administered twice in 4 years correlates with long-term dietary intake patterns is uncertain. Several reviews (McClure et al., 2017; EFSA, 2015) have suggested that dietary intake of P is usually underestimated for the reasons outlined above.

The bioavailability of P from different sources varies widely, as discussed in Section 2.3.3. Oral bioavailability of dietary P depends on the food source (animal or plant derived) and the organic or inorganic form of the P-containing food: bioavailability is lowest for plant sources (10−30%), higher for animal sources (40−60%), and highest for food additives (80−100%), which includes phosphoric acid and several (Na/K) phosphates. Most of the dietary intake studies did not account for different sources of P in the diet, and none of the studies provided estimates of intake for subcategories of dietary P that may be relevant to the assessment of sodium or potassium salts of inorganic phosphates.

As a result of the uncertainties in doses and differing bioavailability of P forms inherent in the dietary intake studies, the studies considered for dose-response assessment for sodium or potassium salts of inorganic phosphates were restricted to those in which a clearly defined test material was administered. These include the controlled human exposure studies, the human colonoscopy preparation studies, and most (but not all) of the animal studies.

A few short-term, controlled-exposure human studies measuring adverse outcomes (Chang et al., 2017; Medoff et al., 2004; Grimm et al., 2001) were identified. These studies ranged in duration from 3 to 6 weeks. Of the three studies, two (Medoff et al., 2004; Grimm et al., 2001) reported that the test material administered to the volunteers, while Chang et al. (2017) reported only that the supplemented P was in the form of food additives provided as commercially available beverages and breakfast bars. Grimm et al. (2001) administered a combination of calcium phosphate ($Ca_5[PO_4]_3OH$) in orange juice and NaH_2PO_4 tablets. Because the supplemental Ca provided by the calcium phosphate may limit the absorption of phosphate, this study also has limitations for dose-response assessment. Finally, Medoff et al. (2004) administered NaH_2PO_4 tablets to a group of patients with chronic constipation, but allowed the patients to vary the dose to improve their response or mitigate side effects. Assigning a clear LOAEL for this study is difficult. For these reasons, the controlled exposure studies are not considered to provide reliable dose-response information and are not considered for use in the derivation.

The human colonoscopy preparation studies appear to offer several advantages. First, the test material (sodium phosphate) is clearly defined, consistent across exposed persons, and of predictable bioavailability. In addition, unlike the dose estimates in dietary intake studies, the prescribed dose of sodium phosphate taken in preparation for colonoscopy is well characterized. The primary disadvantage of the human colonoscopy preparation studies for dose-response assessment is that exposure to inorganic phosphates occurred for only a single day; thus, using these data to derive a provisional reference dose (p-RfD) would necessitate extrapolation from a single-day exposure to subchronic or chronic exposure. Some evidence suggests that intake-related, short-term spikes in serum P may lead to acute insults (e.g., transient decreases in endothelial dysfunction) (Nishi et al., 2015; Shuto et al., 2009) that could accumulate over time and lead to permanent damage or functional changes, despite homeostatic mechanisms that regulate serum P. However, due to the uncertainty in extrapolating from effects of a single day to subchronic or chronic exposure, these data were not selected for use in p-RfD derivation.

Given the limitations articulated above in the human toxicity database, these studies were not used for toxicity value derivation, which instead relies on animal toxicity data. The human toxicity information is used as supporting information: specifically, the estimated effect levels defined by the colonoscopy preparation studies, FDA warnings, and controlled exposure studies were compared with the p-RfDs derived from the animal studies to ensure that the p-RfDs will adequately protect against effects observed in humans exposed for acute and short-term durations.

3.1.1. Derivation of the Subchronic Provisional Reference Dose

The published, peer-reviewed rabbit study by Ritskes-Hoitinga et al. (2004) was selected as the principal study for deriving the subchronic p-RfD for Na/K salts of inorganic phosphates.

Several subchronic animal studies met criteria for inclusion in the assessment (see Table 3A). Among these studies, the lowest LOAEL was 290 mg P/kg-day (HED 120 mg/kg-day) for nephrocalcinosis in rabbits (Ritskes-Hoitinga et al., 2004). LOAELs in the other studies in the database were as high as 1,100 mg P/kg-day (HED 270 mg/kg-day) based on renal, bone, and body-weight effects in rats (Abuduli et al., 2016; Huttunen et al., 2007; Tani et al., 2007; Koshihara et al., 2005; Ritskes-Hoitinga et al., 1989; Hitchman et al., 1979; Datta et al., 1962; Dymsza et al., 1959). One of the two subchronic experiments reported by Datta et al. (1962) lacked information needed to identify a LOAEL, so this experiment was not considered. From the remaining experiments, the five identifying the lowest LOAELs were considered for use in the dose-response assessment: Huttunen et al. (2007), Koshihara et al. (2005), Ritskes-Hoitinga et al. (2004), Ritskes-Hoitinga et al. (1989), and the remaining experiment reported by Datta et al. (1962).

All these studies were limited in examination of toxicological endpoints, mostly focusing on renal, cardiovascular, or bone effects. Candidate points of departure (PODs) from these studies, reported in HEDs (see calculations in study descriptions in Sections 2 and 2.2), are shown in Table 16. As discussed above and shown in the table, all the animal studies included a referent ("control") group with nonzero phosphate intake, because P is an essential nutrient, and a lack of P in the diet is harmful to health. The doses administered to the referent groups are reported in the table but should not be interpreted as NOAELs (due to the lack of a comparison group) and were not considered as candidate PODs.

Table 16. Candidate PODs for Noncancer Dose-Response Assessment of Na/K Salts of Inorganic Phosphates

Species and Study Type	Endpoint	LOAEL (HED) (mg P/kg-d)	Referent Group Dose (HED) (mg P/kg-d)	Reference
Rabbit; dietary exposure to NaH_2PO_4 dihydrate for 8 wk	Nephrocalcinosis, on the basis of significantly increased kidney Ca and P, and significantly increased incidence and severity scores for cortical calcifications	120	63	Ritskes-Hoitinga et al. (2004)
Rat; dietary exposure to NaH_2PO_4 dihydrate for 4 wk	Nephrocalcinosis, on the basis of statistically or biologically significant increases in urine albumin and relative kidney weights	120	86	Ritskes-Hoitinga et al. (1989)
Rat; dietary exposure to KH_2PO_4 for 6 wk	Significantly bmd (fifth lumbar vertebra), significantly increased serum osteocalcin and urinary deoxypyridinoline	200	68	Koshihara et al. (2005)
Rat; dietary exposure to Na_2HPO_4 for 16 wk	Increased relative kidney weight (17−39%); impaired kidney function; increased incidence of renal histopathology (medullary calcification and necrosis, tubular casts, hemorrhages/exudate, chronic inflammatory changes)	200	67	Datta et al. (1962)
Rat; dietary exposure to $CaHPO_4$ and KH_2PO_4 for 8 wk	Significantly decreased body weight (11%) and food intake; significantly decreased bmc and bmd; alterations in several measures of bone histomorphometry; nonsignificant decrease in bone strength.	240	120	Huttunen et al. (2007)

bmc = bone mineral content; bmd = bone mineral density; Ca = calcium; $CaHPO_4$ = calcium phosphate; HED = human equivalent dose; KH_2PO_4 = monopotassium phosphate; LOAEL = lowest-observed-adverse-effect level; Na/K = sodium and potassium; Na_2HPO_4 = disodium phosphate; NaH_2PO_4 = monosodium phosphate; P = phosphorus; POD = point of departure.

The lowest LOAELs (HED) (120 mg P/kg-day) are based on nephrocalcinosis in male rabbits exposed to NaH_2PO_4 in the diet for 8 weeks (Ritskes-Hoitinga et al., 2004) and also in female rats exposed to NaH_2PO_4 in the diet for 4 weeks (Ritskes-Hoitinga et al., 1989). Renal effects were also the basis of the LOAEL (HED) (200 mg P/kg-day) for the subchronic study (Datta et al., 1962), in which rats received Na_2HPO_4 for 16 weeks. The renal effects seen in these studies (nephrocalcinosis, increased kidney weights, impaired kidney function) are similar to the acute and chronic kidney injury (e.g., acute phosphate nephropathy) seen in some human studies after exposure to OSP compounds for colonoscopy preparation. The fact that this potential POD is identical in rats and rabbits adds confidence for nephrocalcinosis as the critical effect and 120 mg/kg-d P as the POD.

LOAEL (HED) values for the other two studies shown in Table 16 (Huttunen et al., 2007; Koshihara et al., 2005) were 240 and 200 mg P/kg-day (respectively) based on decreases in bmd and related parameters. Unlike for renal effects, there is less evidence for parallel changes in bone metabolism in humans exposed to higher dietary intakes of phosphates, although the available literature examining these endpoints suffers from the same limitations as other dietary intake studies. Available information in humans appears to point to *improved* bone health with higher dietary P intake (Jones et al., as cited in EFSA, 2015; Heppe et al., 2013; Yin et al., 2010; Tobias et al., 2005; Elmståhl et al., 1998). Because the bone effects in animals are not clearly reflected in effects seen in humans while renal effects are, and given the lower LOAELs for renal effects, neither Koshihara et al. (2005) nor Huttunen et al. (2007) was considered further for use in the derivation.

Ritskes-Hoitinga et al. (2004), Ritskes-Hoitinga et al. (1989), and Datta et al. (1962) did not include more than one nonreferent dose with suitable data, so these data sets were not amenable to benchmark dose (BMD) modeling. Both Ritskes-Hoitinga et al. (2004) and Ritskes-Hoitinga et al. (1989) identified a LOAEL (HED) value of 120 mg P/kg-day, which is lower than the LOAEL (HED) value from Datta et al. (1962). Thus, these studies were selected for use in deriving the subchronic p-RfD for Na/K salts of inorganic phosphates, and the LOAEL (HED) of 120 mg P/kg-day for increased incidence of nephrocalcinosis in rabbits exposed to NaH_2PO_4 dihydrate for 8 weeks via the diet (Ritskes-Hoitinga et al., 2004) was selected as the POD for derivation of the subchronic p-RfD.

The subchronic p-RfD for extra-dietary exposure to Na/K salts of inorganic phosphates is derived 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 LOAEL-to-NOAEL uncertainty factor [UF_L] of 3) to the selected POD (HED) of 120 mg P/kg-day.

Subchronic p-RfD	=	POD (HED) ÷ UF_C
	=	120 mg P/kg-day ÷ 30
	=	**4 mg P/kg-day as sodium or potassium salts of inorganic phosphates**

Table 17 summarizes the uncertainty factors for the subchronic p-RfD for Na/K salts of inorganic phosphates. Uncertainty factors were applied in accordance with applicable guidance and methodology (U.S. EPA, 2011b, 2002).

Table 17. Uncertainty Factors for the Subchronic p-RfD for Na/K Salts of Inorganic Phosphates

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 Na/K phosphate 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, 2011b).
UF_D	1	A UF_D of 1 is applied in accordance with U.S. EPA (2002), because reproductive and developmental toxicity studies in rats, rabbits, mice, and hamsters are available (see Table 11) and show no indication of effects at doses below those in subchronic and chronic studies. Additionally, numerous short-term, subchronic, and chronic oral studies in several species are available that investigated a variety of health effects. The evidence base also comprises numerous epidemiological studies including controlled exposure studies, cohort and case-control dietary intake studies, and randomized studies of OSP use for bowel preparation or constipation that report health effects.
UF_H	3	A UF_H of 3 ($10^{0.5}$) is applied to account for low human variability in susceptibility to P, due to tightly regulated homeostatic mechanisms in average individuals. Populations with pre-existing kidney disease may be more susceptible. CKD is known to increase susceptibility to inorganic phosphate toxicity, and its prevalence in the United States is around 14% (NIDDK, 2016). However, the differences in susceptibility are modest and are captured in the available human data. For instance, the prospective study by Yoon et al. (2017) found no effect of increased P intake on incidence of CKD in nondiabetic adults followed for 8 yr but did see an increased incidence in CKD in the highest P exposed quartile of diabetics. Support for using a UF_H of 3 is provided by the fact that the p-RfD based on Ritskes-Hoitinga et al. (2004) is more protective than a p-RfD derived based on kidney effects observed in the susceptible (diabetic) population in Yoon et al. (2017) .
UF_L	3	A UF_L of 3 ($10^{0.5}$) is applied because the POD is a LOAEL. The difference between LOAEL and referent group dose in the study was ~twofold, and the incidence of nephrocalcinosis in the referent group was not significantly different than the next lower dose (indicating the referent group approximates a NOAEL). Therefore, a full 10-fold uncertainty factor is not considered appropriate.
UF_S	1	A UF_S of 1 is applied because the subchronic POD is from a subchronic (8-wk) study.
UF_C	30	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

CKD = chronic kidney disease; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; Na/K = sodium and potassium; NOAEL = no-observed-adverse-effect level; OSP = oral sodium phosphate; P = phosphorus; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor; U.S. EPA = U.S. Environmental Protection Agency.

Confidence in the subchronic p-RfD for Na/K salts of inorganic phosphates is medium, as described in Table 18.

Table 18. Confidence Descriptors for the Subchronic p-RfD for Na/K Salts of Inorganic Phosphates

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study is medium. Ritskes-Hoitinga et al. (2004) exposed small groups (eight per dose) of male rabbits for 8 wk to diets containing four different P concentrations, but only two contained at least the minimum level of P (0.4%) recommended for rabbits (Clarke et al., 1977). However, the study used a well-characterized diet and controlled for dietary Ca. In addition, the renal endpoint (nephrocalcinosis) and POD are supported by a similar study in rats (Ritskes-Hoitinga et al., 1989). Endpoints tested in these studies, although limited compared with a comprehensive subchronic toxicity study, included sensitive endpoints known or believed to be associated with phosphate intake. Endpoints included body weight/growth and feed intake, urine and fecal mineral content, weight and histology of the kidney, and femur dimensions and mineral content.
Confidence in database	M	Confidence in the database is medium. The database comprises numerous epidemiological studies including controlled exposure studies, cohort and case-control dietary intake studies, and randomized studies of OSP use for bowel preparation or constipation that report a variety of health effects. Although the database includes many human studies, these suffer from several limitations, including uncertainty in doses and relevance of dietary P (i.e., organic and inorganic sources of P). The database also contains short-term, subchronic, and chronic oral studies in rats, rabbits, and dogs that report a variety of health effects. Although animal data are extensive, many studies are limited by a lack of information on concurrent Ca intake, a key determinant of phosphate toxicity. Reproductive and developmental toxicity screening studies in rats, rabbits, mice, and hamsters are also available (see Table 11), although many studies are technical reports or reported only in secondary publications.
Confidence in subchronic p-RfD	M	Overall confidence in the subchronic p-RfD is medium.

Ca = calcium; L = low; M = medium; Na/K = sodium and potassium; OSP = oral sodium phosphate; P = phosphorus; p-RfD = provisional reference dose.

3.1.2. Derivation of the Chronic Provisional Reference Dose

As shown in Table 3A, none of the available chronic animal studies of Na/K salts of inorganic phosphates met selection criteria. Thus, the chronic p-RfD for extra-dietary exposure to Na/K salts of inorganic phosphates is derived from the same POD as the subchronic p-RfD—the LOAEL (HED) of 120 mg P/kg-day for increased incidence of nephrocalcinosis in rabbits exposed to NaH_2PO_4 dihydrate for 8 weeks via the diet (Ritskes-Hoitinga et al., 2004)—by applying a UF_C of 100 (reflecting a UF_A of 3, a UF_H of 3, a UF_L of 3 for using a LOAEL, and a subchronic-to-chronic extrapolation uncertainty factor [UF_S] of 3 for use of a subchronic LOAEL as a POD).

Chronic p-RfD	=	POD (HED) ÷ UF_C
	=	120 mg P/kg-day ÷ 100
	=	**1 mg P/kg-day as sodium or potassium salts of inorganic phosphates**

Table 19 summarizes the uncertainty factors for the chronic p-RfD for Na/K salts of inorganic phosphates. Uncertainty factors were applied in accordance with applicable guidance and methodology (U.S. EPA, 2011b, 2002).

Table 19. Uncertainty Factors for the Chronic p-RfD for Na/K Salts of Inorganic Phosphates

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 Na/K phosphate 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, 2011b).
UF_D	1	A UF_D of 1 is applied as reproductive and developmental toxicity studies in rats, rabbits, mice, and hamsters are available (see Table 11), including a three-generation reproductive toxicity study, which do not signal concern for effects on fertility or development at levels below the POD for kidney effects in the principal study. The evidence base also contains short-term, subchronic, and chronic oral studies in rats and rabbits that investigate a variety of health effects. Regarding human data, numerous epidemiological studies have been conducted that investigate a variety of health effects, although methodological concerns limit their use for estimating effect levels for Na/K inorganic phosphates.
UF_H	3	A UF_H of 3 ($10^{0.5}$) is applied to account for low human variability in susceptibility to increased P, due to tightly regulated homeostatic mechanisms in average individuals. Populations with pre-existing kidney disease may be more susceptible. CKD is known to increase susceptibility to inorganic phosphate toxicity, and its prevalence in the United States is around 14% (NIDDK, 2016). However, the differences in susceptibility are modest and are captured in the available human data. For instance, the prospective study by Yoon et al. (2017) found no effect of increased P intake on incidence of CKD in nondiabetic adults followed for 8 yr but did see an increased incidence in CKD in the highest P exposed quartile of diabetics. Support for using a UF_H of 3 is provided by the fact that the p-RfD based on Ritskes-Hoitinga et al. (2004) is more protective than a p-RfD derived based on kidney effects observed in the susceptible (diabetic) population in Yoon et al. (2017).
UF_L	3	A UF_L of 3 ($10^{0.5}$) is applied because the POD is a LOAEL. The difference between LOAEL and referent group dose in the key study was ~twofold, and the incidence of nephrocalcinosis in the referent group was not significantly higher than the next lower dose (indicating the referent group approximates a NOAEL). Therefore, a full 10-fold UF was not considered appropriate.
UF_S	3	A UF_S of 3 ($10^{0.5}$) was applied to address the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure. The POD was derived from an 8-wk study in rabbits (Ritskes-Hoitinga et al., 2004), which observed increased Ca deposits in the kidney. It is possible that longer exposure durations could result in increased severity of kidney effects or effects seen at lower doses. However, a full uncertainty factor of 10 was not considered appropriate due to the narrow dose range between the POD for kidney toxicity (0.88% P) and the recommended (lower bound) P intake in rabbits to meet nutritional needs (0.22% P)(NRC, 1977).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

Ca = calcium; CKD = chronic kidney disease; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; Na/K = sodium and potassium; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor; U.S. EPA = U.S. Environmental Protection Agency.

Confidence in the chronic p-RfD for the Na/K salts of inorganic phosphates is medium, as described in Table 20.

Table 20. Confidence Descriptors for the Chronic p-RfD for Na/K Salts of Inorganic Phosphates

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal studies is medium. Ritskes-Hoitinga et al. (2004) exposed small groups (eighty per dose) of male rabbits to diets containing four different P concentrations, but only two contained at least the minimum level of P (0.4%) recommended for rabbits (Clarke et al., 1977). However, the study used a well-characterized diet and controlled for dietary Ca. In addition, the renal endpoint (nephrocalcinosis) and POD is supported by a similar study in rats by Ritskes-Hoitinga et al. (1989). Endpoints tested in the studies, although limited compared with a comprehensive toxicity study, included sensitive endpoints known or believed to be associated with phosphate intake. Endpoints included body weight/growth and feed intake, urine and fecal mineral content, weight and histology of the kidney, and femur dimensions and mineral content.
Confidence in database	M	Confidence in the database is medium. The database comprises numerous epidemiological studies including controlled exposure studies, cohort and case-control dietary intake studies, and randomized studies of OSP use for bowel preparation or constipation that report a variety of health effects. Although the database includes many human studies, these suffer from several limitations, including uncertainty in doses and relevance of dietary P (i.e., organic or inorganic P). The database also contains short-term, subchronic, and chronic oral studies in rats, rabbits, and dogs that report a variety of health effects. Although animal data are extensive, many studies are limited by a lack of information on concurrent Ca intake, a key determinant of phosphate toxicity. Reproductive and developmental toxicity screening studies in rats, rabbits, mice, and hamsters are also available (see Table 11), although many studies are technical reports or reported only in secondary publications.
Confidence in chronic p-RfD	M	Overall confidence in the chronic p-RfD is medium.

Ca = calcium; L = low; M = medium; Na/K = sodium and potassium; OSP = oral sodium phosphate; P = phosphorus; p-RfD = provisional reference dose.

3.1.3. Consideration of Human Data

As discussed above, information from human studies and FDA warnings, while inadequate for dose-response assessment, provides clear not-to-exceed dose estimates that may be used to assess whether the derived p-RfDs will be adequately protective for effects observed after acute and short-term durations. In addition, the relevance of the Recommended Daily Intake (RDI) of P, typical intake in the United States, and human subpopulations known to be more susceptible to phosphate toxicity warrant discussion.

Table 21 provides a comparison between the subchronic and chronic p-RfDs for Na/K salts of inorganic phosphates and effect levels identified in 1-day and short-term exposure studies in humans exposed to sodium or potassium phosphates. The table shows the study, exposure duration, estimated LOAEL, and margins of safety calculated as the ratios of the LOAEL to the subchronic p-RfD. As the table demonstrates, the p-RfD values derived from animal toxicity data provide adequate protection against effects seen in humans after acute or short-term exposure.

Table 21. Comparison between Subchronic p-RfD and LOAELs from Acute and Short-Term Human Exposures to Na/K Salts of Inorganic Phosphates

Reference and Study Type	Exposure Duration	Endpoint	LOAEL (mg P/kg-d as inorganic phosphate)	Margin of Safety (human LOAEL/subchronic p-RfD)
Nishi et al. (2015); controlled exposure	1 d	Transient decrease in vascular endothelial function compared with pre-exposure levels	26.49	7
FDA (2014); warning re: constipation therapy	1−3 d	Laxative effect, with severe effects occurring at higher doses	40−105 (not including dietary intake)	>10
Grimm et al. (2001); controlled exposure	4−6 wk	GI disturbances	50.13	13
Colonoscopy preparation[a]: Hurst et al. (2007) prospective cohort study, FDA (2008) warning, and numerous other studies and case reports	1 d	Increased risk of acute renal failure/acute phosphate nephropathy; GI distress (nausea, diarrhea, bloating, vomiting) during bowel preparation for colonoscopy	164	41

[a]Standard dose is administered in <24 hours (usually 10−12 hours apart). Dose is assumed to reflect all P sources during the day of preparation, but small amounts of P may also be consumed if allowed foods (e.g., gelatin desserts) contain P.

GI = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; Na/K = sodium and potassium; P = phosphorus; p-RfD = provisional reference dose.

FDA (2014) and FDA (2008) issued health warnings pertaining to the use of OSP preparations for bowel cleansing and treatment of constipation. The 2008 warning pertained to acute kidney injury associated with bowel cleansing, and this effect and its LOAEL are shown in Table 21 with corresponding margins of safety. The 2014 FDA warning pertained to severe dehydration, electrolyte imbalances, and serious effects on the heart and kidneys, sometimes leading to death in individuals (including children) who exceed recommended daily doses of sodium phosphate preparations for constipation therapy. As discussed further in Section 2.1, the therapeutic recommendations correspond to P intakes of ~40−100 mg P/kg-day (for up to 3 days) as sodium phosphate for children >5 years of age and adults. The derived p-RfD values are well below these intake levels. FDA (2014) recommended against any use of sodium phosphate colonoscopy therapeutics for infants and children under 5 years of age unless under physician supervision; further discussion of these and other susceptible populations is presented after the discussion of nutritional requirements below.

Phosphorus is an essential nutrient that exhibits a U-shaped dose-response curve: doses below physiological requirements may lead to deleterious effects, as can doses that exceed physiological requirements. The RDI value for P is 700 mg P/day or 10 mg P/kg-day for a 70-kg adult (EFSA, 2015; IOM, 1997). Note however, that the RDI includes P from less bioavailable and organic plant and animal sources in addition to other poorly absorbed inorganic phosphate

sources. Furthermore, dietary intake of P in the U.S. population is more than adequate; based on NHANES data between 2001 and 2014, McClure et al. (2017) estimated mean dietary P intake over the entire period to be 1,373 mg P/day (range of means by year was 1,324−1,414 mg P/day), or ~20 mg P/kg-day for a 70-kg adult. Although little information regarding the proportion of total dietary P load from inorganic phosphate additives (the source most relevant to this assessment) was located, one source estimated the contribution to be ~500 mg P/day (Calvo et al., 2013 as cited in Trautvetter et al., 2018). Given that the RDI of P includes both organic and inorganic sources, and extra-dietary environmental exposure to (highly bioavailable) Na/K salts of inorganic phosphate will increase P intake over and above a dietary intake that is more than adequate, the RDI is not considered to be a lower bound on the p-RfD for the Na/K salts of inorganic phosphates.

A significant proportion of the U.S. population may exhibit conditions or characteristics that increase their susceptibility to phosphate toxicity. For example, CKD impairs the body's ability to excrete excess P, leading to hyperphosphatemia. As a result, people with CKD may be prescribed phosphate binders or instructed to reduce their intake of dietary P below the values recommended for healthy persons. Approximately 14% of the U.S. population has CKD (NIDDK, 2016). Populations on dialysis are particularly susceptible to increases in P, with one study indicating disruption of P homeostasis and activation of markers of bone resorption in patients with increased dietary intake of 100 mg/d (Tsai et al., 2021). Additional characteristics that may increase susceptibility to phosphate toxicity include female sex, low body mass index (BMI), dehydration, use of ACEIs or diuretics, and older age (FDA, 2014). Finally, as noted above, FDA recommends against the use of sodium phosphate compounds to treat constipation in infants and children under 5 years of age, unless under physician supervision, due to their enhanced susceptibility.

In deriving the p-RfDs presented herein, every effort was made to ensure that the resulting values would provide adequate protection against phosphate toxicity while working within the limitations of available data and U.S. EPA methodologies. However, Na/K salts of inorganic phosphates present unique challenges in toxicity value derivation, among them the large number of potentially susceptible individuals and high background intake of both P and inorganic phosphate additives in the U.S. population.

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

3.2.1. Derivation of the Subchronic Provisional Reference Concentration

Relevant data with which to derive a subchronic provisional reference concentration (p-RfC) for Na/K salts of inorganic phosphates were not identified in the available literature. As noted earlier, the studies of workers involved in phosphate mining and fertilizer production (Yiin et al., 2016; Khelifi et al., 2014) are confounded by coexposure to a host of other hazardous and radioactive substances.

3.2.2. Derivation of the Chronic Provisional Reference Concentration

For phosphoric acid, a chronic inhalation reference concentration (RfC) of 0.01 mg/m^3 is available in U.S. EPA's IRIS database (U.S. EPA, 1995). This RfC is based on a subchronic study (Aranyi et al., 1988) of rats exposed to an aerosol of combustion products from burning 95% red phosphorus and 5% butyl rubber. Uncertainty with respect to the toxicology of the exposure mixture precludes using that study as the basis for a p-RfC. No relevant human or

animal studies of inorganic phosphate inhalation published since the 1995 assessment were identified in the literature searches or secondary sources reviewed.

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

A summary of the noncancer provisional reference values is shown in Table 22.

Table 22. Summary of Noncancer Risk Estimates for Na/K Salts of Inorganic Phosphates (Multiple CASRNs)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg P/kg-d as Na/K salts of inorganic phosphates)	Rabbit/M;	Nephro-calcinosis	4×10^0	LOAEL	120	30	Ritskes-Hoitinga et al. (2004);
Chronic p-RfD (mg P/kg-d as Na/K salts of inorganic phosphates)	Rabbit/M;	Nephro-calcinosis	1×10^0	LOAEL	120	100	Ritskes-Hoitinga et al. (2004);
Subchronic p-RfC (mg P/m^3)	NDr						
Chronic p-RfC (mg P/m^3)	An RfC for phosphoric acid is available on IRIS (U.S. EPA, 1995).[a]						

[a]Based on bronchiolar fibrosis in rats exposed by inhalation for 13 weeks.

HED = human equivalent dose; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; M = male; Na/K = sodium and potassium; NDr = not determined; P = phosphorus; p-RfC = provisional inhalation reference concentration; p-RfD = provisional oral reference dose; POD = point of departure; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Human data pertinent to the assessment of Na/K salts of inorganic phosphate carcinogenicity are limited to cohort and case-control studies of dietary P intake (see Tables 9 and 10). These studies suffer from many of the same limitations noted in dietary intake studies of noncancer endpoints, including variability in the bioavailability of different P sources and lack of data on intake for subcategories of dietary P that may be relevant to the assessment of Na/K salts of inorganic phosphates. A well-conducted, large prospective cohort study (Wilson et al., 2015) observed increased risk of prostate cancer, especially lethal and high-grade cancers, with higher dietary intake of P, after controlling for Ca, dairy, and animal protein intake. Three other dietary intake cohort studies and a case-control study examined associations with prostate cancer but did not find any significant associations. All three negative cohort studies were limited by very brief follow-up times (~8 years on average) compared with Wilson et al. (2015) (24 years).

No studies examined cancer endpoints in animals exposed to sodium or potassium salts of inorganic phosphates by oral or inhalation routes. Available genotoxicity data indicate that sodium or potassium salts of inorganic phosphates are not mutagenic and do not induce CAs or DNA damage in vitro, nor mutations in vivo (see Section 2.3.1). Wilson et al. (2015) suggested that P could influence prostate cancer progression via increases in PTH that increase bone

remodeling, leading to an increase in the metastasis of prostate tumors to bone, but confirmatory or supporting data were not identified in the literature.

Although the study by Wilson et al. (2015) addressed several limitations of previous human studies, its relevance to the carcinogenicity of Na/K salts of inorganic phosphates remains uncertain, as the proportion of the dietary intake corresponding to inorganic phosphates relevant to the compounds under assessment is not known. In addition, the increases in RR of prostate cancer observed by Wilson et al. (2015) were small; adjusted RRs were ≤1.13 for all prostate cancers and ≤1.51 for lethal and high-grade cancers. Finally, animal and mechanistic data supporting an association with prostate cancer are lacking. Thus, the available data are not considered adequate to assess the carcinogenicity of Na/K salts of inorganic phosphates.

The cancer weight-of-evidence (WOE) descriptor for Na/K salts of inorganic phosphates is shown in Table 23.

Table 23. Cancer WOE Descriptor for Na/K Salts of Inorganic Phosphates

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	The available data do not support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**Existing information is inadequate to evaluate the carcinogenicity of Na/K salts of inorganic phosphate compounds in humans or animals.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

NA = not applicable; Na/K = sodium and potassium; NS = not selected; WOE = weight of evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

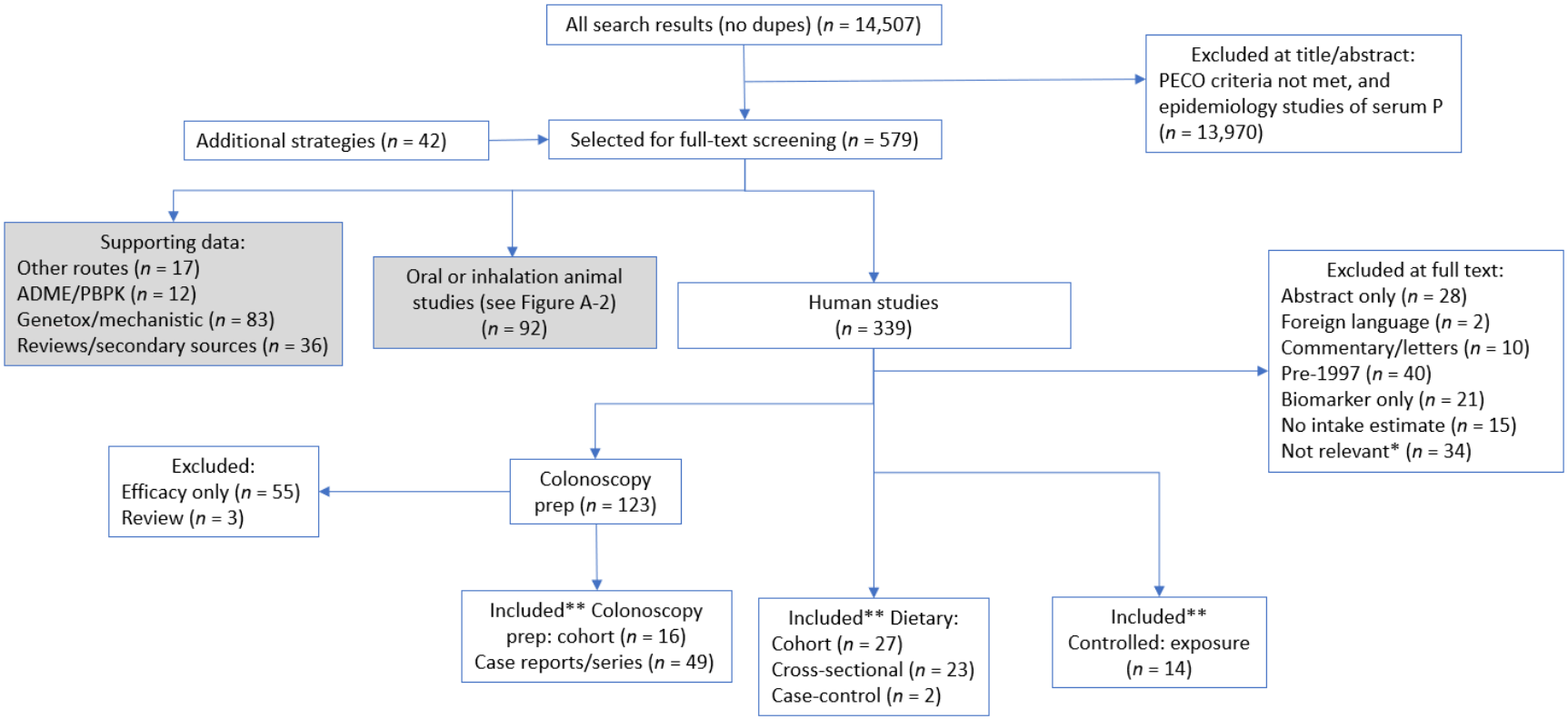
Derivation of quantitative estimates of cancer risk for Na/K salts of inorganic phosphates is precluded by the lack of data demonstrating carcinogenicity associated with exposure (see Table 24).

Table 24. Summary of Cancer Risk Estimates for Na/K Salts of Inorganic Phosphates (Multiple CASRNs)

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

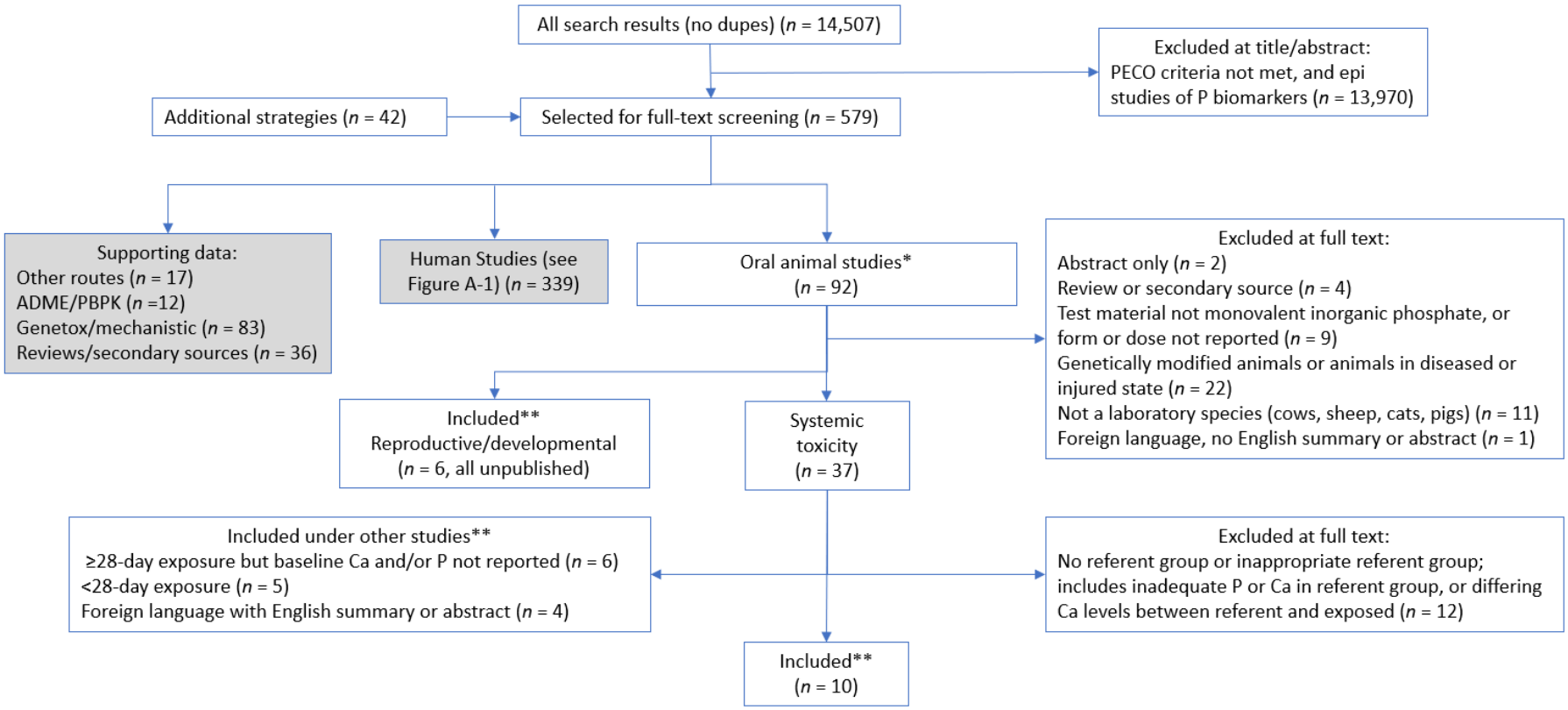
Na/K = sodium and potassium; NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. LITERATURE SCREENING RESULTS



*Treatment of hypophosphatemia, effects of phosphate restriction, cotreatment with other agent, pathological hyperphosphatemia, no comparison group, inappropriate route, performance enhancement.
**Includes studies discussed in text, in addition to those tabulated and formally evaluated. Not all included studies are cited.

Figure A-1. Literature Screening Results: Human Studies



*No animal studies using inhalation exposure were identified.
**Includes studies discussed in text in addition to those tabulated and formally evaluated. All included studies are cited.

Figure A-2. Literature Screening Results: Animal Studies

APPENDIX B. DATA TABLES

Table B-1. Significant Effects in Female Weanling Wistar Rats Administered Inorganic Phosphate (as $Ca[H_2PO_4]_2$ Alone or with NaH_2PO_4) in the Diet for 6 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)	
	530 (0.5% P in diet; referent)	1,100 (1% P in diet)
Kidney Ca concentration (µg/g)	460 ± 167[b]	3,350 ± 470* (+628%)[c]
Kidney wet weight (g)	1.87 ± 0.04	2.16 ± 0.11* (+16%)

[a]Hitchman et al. (1979).
[b]Mean ± SE.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from referent group at $p < 0.05$, based on two-sided *t*-test performed for this review.

Ca = calcium; $Ca[H_2PO_4]_2$ = Calcium phosphate; NaH_2PO_4 = monosodium phosphate; P = phosphorus; SE = standard error.

Table B-2. Significant Effects in Male Wistar Rats Administered Inorganic Phosphate (as $CaHPO_4$ and KH_2PO_4) in the Diet for 8 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)		
	510 (0.6% P in diet; referent)	980 (1.2% P in diet)	1,400 (1.8% P in diet)
Serum PTH (units not specified)	300 ± 166[b]	583 ± 272 (+94%)[c]	2,190 ± 821** (+630%)[c]
Femur length (cm)	3.7 ± 0.14	3.6 ± 0.19 (−3%)	3.4 ± 0.15** (−8%)
Femur bmc; final (g)	0.35 ± 0.03	0.33 ± 0.03 (−6%)	0.28 ± 0.03** (−20%)
Femur bmd; final (g/cm^3)	0.23 ± 0.02	0.21 ± 0.02** (−9%)	0.19 ± 0.02** (−17%)
Femur; distal metaphysis			
Total bone bmc (g)	11.3 ± 0.90	9.6 ± 0.92** (−15%)	9.8 ± 1.12** (−13%)
Total bone CSA (mm^2)	19.9 ± 2.3	17.9 ± 1.3* (−10%)	17.3 ± 2.4** (−13%)
Cortical bmc (g)	8.04 ± 0.46	7.34 ± 0.64* (−9%)	7.03 ± 0.76** (−13%)
Cortical CSA (mm^2)	7.7 ± 0.3	7.1 ± 0.2** (−8%)	7.6 ± 0.3* (−1%)
Femur; midshaft			
Total bone bmc (g)	8.5 ± 0.67	7.9 ± 0.54* (−7%)	7.0 ± 0.69** (−18%)
Total bone CSA (mm^2)	10.8 ± 1.3	9.8 ± 0.8* (−9%)	9.4 ± 0.7** (−13%)
Cortical bmd (g/cm^3)	1,289.2 ± 12.5	1,291.0 ± 15.6 (+0%)	1,250.1 ± 19.2** (−3%)
Cortical bmc (g)	7.74 ± 0.56	7.18 ± 0.49* (−7%)	6.32 ± 0.69** (−18%)
Cortical CSA (mm^2)	6.0 ± 0.5	5.6 ± 0.4* (−7%)	5.0 ± 0.5** (−17%)
Cortical thickness (mm)	0.72 ± 0.43	0.70 ± 0.35 (−3%)	0.65 ± 0.46** (−10%)

Table B-2. Significant Effects in Male Wistar Rats Administered Inorganic Phosphate (as $CaHPO_4$ and KH_2PO_4) in the Diet for 8 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)		
	510 (0.6% P in diet; referent)	980 (1.2% P in diet)	1,400 (1.8% P in diet)
Femur; mechanical competence			
Ultimate strength (N)	117 ± 8.6	104 ± 7.4 (−10%)	88.3 ± 18** (−24%)
Yield point	100 ± 9.2	80 ± 20 (−20%)	64 ± 25** (−36%)
Tibia; trabecular bone			
Bone volume (mm^3)	2.5 ± 0.3†	1.2 ± 0.2 (−52%)	1.7 ± 0.4 (−32%)
Bone surface (mm^2)	141 ± 8.1†	75 ± 14 (−47%)	97 ± 18 (−31%)
Structure model index	2.1 ± 0.10†	2.1 ± 0.03 (+0%)	1.8 ± 0.05 (−14%)
Connective structures per unit volume (mm^{-3})	46.4 ± 14	37.9 ± 0.79 (−18%)	69.9 ± 2.28 (+51%)
Tibia; cortical bone			
Total cross-sectional area (mm^2)	5.3 ± 0.24‡	4.5 ± 0.14 (−15%)	4.0 ± 0.06 (−25%)
Tibia; mechanical competence			
Ultimate strength (N)	118 ± 18‡	104 ± 8.7 (−12%)	83 ± 14 (−30%)
Stiffness (N/mm)	332 ± 51‡	295 ± 23 (−11%)	251 ± 49 (−24%)
Toughness (N-M × 10^{-3})	103 ± 17‡	71 ± 18 (−32%)	62 ± 23 (−40%)
Yield point	74 ± 19†	81 ± 18 (+9%)	56 ± 20 (−24%)

[a]Huttunen et al. (2007).
[b]Mean ± SD.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from the referent group at $p \leq 0.05$, based on pairwise analyses performed by the study authors.
**$p \leq 0.01$.
†Significant difference across all groups by ANOVA at $p \leq 0.05$, as reported by the study authors.
‡$p \leq 0.01$.

ANOVA = analysis of variance; bmc = bone mineral content; $CaHPO_4$ = calcium phosphate; CSA = cross-sectional area; KH_2PO_4 = monopotassium phosphate; N = newtons; N-M = newton meters (units of toughness); P = phosphorus; PTH = parathyroid hormone; SD = standard deviation.

Table B-3. Significant Effects in Female Wistar Rats Administered Inorganic Phosphate (as KH_2PO_4) in the Diet for 6 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)	
	270 (0.5% P in diet; referent)	800 (1.5% P in diet)
Body-weight gain (g)	32.27 ± 2.69[b]	28.65 ± 2.88 (−11%)[c]
Ca absorption (mg/d)	14.29 ± 1.52	5.57 ± 3.23* (−61%)
P balance		
Absorption (mg/d)	38.78 ± 1.30	148.40 ± 5.41* (+283%)
Urinary excretion (mg/d)	29.36 ± 5.83	115.59 ± 6.86* (+294%)
Serum osteocalcin (ng/mL)	20.05 ± 1.50	27.88 ± 2.53* (+39%)
Urinary deoxypyridinoline (nmol/mmol creatinine)	70.76 ± 5.44	89.60 ± 7.16* (+27%)
Fifth lumbar bmd (mg/cm^2)	78.02 ± 0.77	71.87 ± 0.88* (−8%)

[a]Koshihara et al. (2005).
[b]Mean ± SEM for *n* = five per group.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from referent group at $p < 0.05$, based on analyses performed by the study authors.

bmd = bone mineral density; Ca = calcium; KH_2PO_4 = monopotassium phosphate; P = phosphorus; SEM = standard error of the mean.

Table B-4. Effects in Female Wistar RIV:TOX Rats Administered Inorganic Phosphate in the Diet (as NaH_2PO_4 Dihydrate) for 28 Days (Experiment 1)[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)	
	390 (0.41% P in diet; referent)	580 (0.60% P in diet)
Body weight (g)	89.4 ± 10.4[b]	90.7 ± 8.4 (+1%)[c]
Urine pH		
Study Days 0−2	9.2 ± 0.1	8.5 ± 0.8** (−8%)
Study Days 13−15	8.3 ± 0.7	7.5 ± 0.6* (−10%)
Study Days 26−28	8.8 ± 0.6	7.3 ± 0.3** (−17%)
Urine albumin (mg/d)		
Study Days 13−15	0.52 ± 0.17	1.45 ± 0.71** (+179%)
Study Days 26−28	0.56 ± 0.29	0.99 ± 0.40* (+77%)
Urine urea (mg/100 g body weight × d)		
Study Days 13−15	157.8 ± 24.6	185.3 ± 33.9* (+17%)
Study Days 26−28	177.7 ± 21.8	189.4 ± 28.5 (+7%)
Relative kidney weight (g/100 g body weight)	0.41 ± 0.04	0.52 ± 0.08** (+27%)
Kidney P (%)	1.5 ± 0.2	3.7 ± 1.3** (+2%)
Kidney Ca (%)	0.4 ± 0.2	5.7 ± 3.0** (+5%)
Kidney Mg (%)	0.10 ± 0.00	0.23 ± 0.07** (+0.1%)
Nephrocalcinosis	2/6[d] (33%)	16/16 (100%)
Mean severity	0.5	2.7†

[a]Ritskes-Hoitinga et al. (1989).
[b]Mean ± SD.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100, or for data presented as percent, it is percent difference = (treatment mean % − control mean %).
[d]Number affected/number examined (% incidence).
*Significantly different from referent group at $p < 0.05$, based on analyses performed by the study authors.
**$p < 0.01$.
†The distribution of histological scores was significantly different from that of the reference group at $p < 0.05$, based on analyses (Mann-Whitney U test) performed by the study authors.

Ca = calcium; Mg = magnesium; NaH_2PO_4 = monosodium phosphate; P = phosphorus; SD = standard deviation.

Table B-5. Effects in Female Wistar RIV:TOX Rats Administered Inorganic Phosphate in the Diet (as NaH_2PO_4 Dihydrate) for 28 Days (Experiment 2)[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)	
	410 (0.41% P in diet; referent)	580 (0.61% P in diet)
Body weight (g)	87.2 ± 4.1[b]	88.5 ± 6.5 (+1%)[c]
Urine pH		
Study Days 0−2	8.9 ± 0.4	8.2 ± 0.4** (−8%)
Study Days 13−15	8.6 ± 0.6	7.7 ± 0.7** (−10%)
Study Days 26−28	8.5 ± 0.8	7.9 ± 0.9 (−7%)
Urine albumin (mg/d)		
Study Days 0−2	0.15 ± 0.07	0.10 ± 0.03* (−33%)
Study Days 13−15	0.22 ± 0.11	0.74 ± 0.55** (+236%)
Study Days 26−28	0.35 ± 0.15	0.60 ± 0.33 (+71%)
Serum Ca (mg/100 mL)	10.21 ± 0.14	9.63 ± 0.45* (−6%)
Serum Mg (mg/100 mL)	2.04 ± 0.15	1.66 ± 0.19* (−18%)
Relative kidney weight (g/100 g body weight)		
Study Day 14	0.45 ± 0.02	0.49 ± 0.07 (+9%)
Study Day 28	0.37 ± 0.03	0.46 ± 0.14 (+24%)
Kidney P (%)		
Study Day 14	1.2 ± 0.0	2.7 ± 1.1** (+2%)
Study Day 28	1.3 ± 0.2	2.4 ± 1.1 (+1%)
Kidney Ca (%)		
Study Day 14	0.1 ± 0.0	3.4 ± 1.9** (+3%)
Study Day 28	0.9 ± −0.8	3.5 ± 2.1* (+3%)
Kidney Mg (%)		
Study Day 14	0.09 ± 0.00	0.18 ± 0.09* (+0.09%)
Study Day 28	0.08 ± 0.00	0.13 ± 0.04* (+0.05%)

Table B-5. Effects in Female Wistar RIV:TOX Rats Administered Inorganic Phosphate in the Diet (as NaH_2PO_4 Dihydrate) for 28 Days (Experiment 2)[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)	
	410 (0.41% P in diet; referent)	580 (0.61% P in diet)
Nephrocalcinosis		
Study Day 14	5/6[d] (83%)	6/6[d] (100%)
Mean severity	1.0	2.8†
Study Day 28	5/6 (83%)	6/6 (100%)
Mean severity	1.5	2.5†

[a]Ritskes-Hoitinga et al. (1989).
[b]Mean ± SD.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100, or for data presented as percent, it is percent difference = (treatment mean % − control mean %).
[d]Number affected/number examined (% incidence).
*Significantly different from referent group at $p < 0.05$, based on analyses performed by the study authors.
**$p < 0.01$.
†The distribution of histological scores was significantly different from that of the reference group at $p < 0.05$, based on analyses performed by the study authors.

Ca = calcium; Mg = magnesium; NaH_2PO_4 = monosodium phosphate; P = phosphorus; SD = standard deviation.

Table B-6. Significant Effects in Male NZW Rabbits Administered Inorganic Phosphate (as NaH_2PO_4 Dihydrate) in the Diet for 8 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)		
	77 (0.2% P in diet)	150 (0.45% P in diet)	290 (0.85% P in diet)
Initial body weight (kg)	1.77 ± 0.10	1.77 ± 0.10[b,c]	1.77 ± 0.10 (+0%)
Final body weight (kg)	2.42 ± 0.41	2.66 ± 0.27	2.41 ± 0.29 (−9%)
Feed intake (g/d)	66.9 ± 9.4	73.1 ± 7.6	68.9 ± 9.5 (−6%)
Urine pH Days 20−23	9.42[b] ± 0.16	9.36 ± 0.15	8.20 ± 0.35* (−1,450%)[d]
Urine pH Days 48−51	9.23[b] ± 0.34	9.35 + 0.23	8.04 + 0.30* (−1,620%)[d]
Urinary Ca	96.8 + 16.7	49.6 + 23.5	1.48 + 0.43* (−3,350%)
Urinary P	22.4 + 5.8	73.4 + 12.6	238 + 23* (+326%)
Serum P (Day 28/Day 56)	1.92 + 0.19/1.80 + 0.28	2.06 + 0.17/1.84 + 0.12	2.51 + 0.63/2.29 + 0.57 (+17.9%/+19.7%)
Serum Ca (Day 28/Day 56)	2.97 + 0.34/3.16 + 0.09	2.81 + 0.29/3.21 + 0.41	2.55 + 0.23/2.71 + 0.20 (−9.0%/−16.6%)
Serum Mg (Day 28/Day 56)	0.63 + 0.09/0.64 + 0.01	0.68 + 0.07/0.63 + 0.18	0.65 + 0.23/0.64 + 0.18 (−4.4%/−2.7%)
Kidney Ca concentration (% dry weight)	0.07 ± 0.04	0.34 ± 0.65	1.40 ± 1.51* (+412%)

Table B-6. Significant Effects in Male NZW Rabbits Administered Inorganic Phosphate (as NaH_2PO_4 Dihydrate) in the Diet for 8 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)		
	77 (0.2% P in diet)	**150 (0.45% P in diet)**	**290 (0.85% P in diet)**
Kidney P concentration (% dry weight)	1.50 + 0.10	1.61 + 0.15	2.08 + 0.60 (+29.2%)
Absolute kidney wet weight (g)	7.34 + 1.41	8.71 + 1.63	8.12 + 1.17 (−6.77)
Absolute kidney dry weight (g)	1.44 ± 0.19	1.60 ± 0.25	1.46 ± 0.16 (−9%)
Relative kidney weight (% body weight)	0.31 ± 0.05	0.33 ± 0.06	0.34 ± 0.05 (+3%)
Diaphysis of femur Mg concentration			
% dry weight	0.40 ± 0.02	0.42 ± 0.01	0.48 ± 0.04* (+14%)
% ash	0.52 ± 0.03	0.55 ± 0.02	0.64 ± 0.05* (+16%)
Epiphysis of femur Mg concentration			
% dry weight	0.24 ± 0.02	0.23 ± 0.04	0.29 ± 0.03* (+26%)
% ash	0.47 ± 0.02	0.47 ± 0.03	0.59 ± 0.07* (+26%)
mg/cm^3	2.26 ± 0.28	2.30 ± 0.42	2.90 ± 0.76* (+26%)
Incidence and severity[e] of renal Ca deposits in the cortex (von Kossa stained)			
0	6/8 (75%)	5/8[f] (63%)	0/8[e] (0%)†
1	2/8 (25%)	2/8 (25%)	3/8 (38%)†
2	0/8 (0%)	1/8 (13%)	4/8 (50%)†
3	0/8 (0%)	0/8 (0%)	1/8 (13%)†
Incidence and severity[e] of renal Ca deposits in the cortex (hematoxylin-eosin stained)			
0	6/8 (75%)	6/8[f] (75%)	0/8[e] (0%)†
1	2/8 (25%)	1/8 (13%)	3/8 (38%)†
2	0/8 (0%)	1/8 (13%)	4/8 (50%)†
3	0/8 (0%)	0/8 (0%)	1/8 (13%)†
Incidence and severity[e] of renal Ca deposits in the medulla (von Kossa stained)			
0	5/8 (63%)	0/8 (0 %)	0/8 (0%)
1	2/8 (25%)	1/8 (13%)	1/8 (13%)
2	1/8 (13%)	6/8 (75%)	7/8 (88%)
3	0/8 (0%)	0/8 (0%)	0/8 (0%)

Table B-6. Significant Effects in Male NZW Rabbits Administered Inorganic Phosphate (as NaH_2PO_4 Dihydrate) in the Diet for 8 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)		
	77 (0.2% P in diet)	**150 (0.45% P in diet)**	**290 (0.85% P in diet)**
Incidence and severity[e] of renal Ca deposits in the medulla (hematoxylin-eosin stained)			
0	3/8 (38%)	0/8 (0%)	0/8 (0%)
1	3/8 (38%)	3/8 (38%)	3/8 (38%)
2	2/8 (25%)	5/8 (63%)	5/8 (63%)
3	0/8 (0%)	0/8 (0%)	0/8 (0%)

[a]Ritskes-Hoitinga et al. (2004).
[b]Mean ± SD for n = eight per group.
[c]Value in parentheses is percent change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Significantly different from the two other groups ($p < 0.05$), based on analyses performed by the study authors (Tukey B test).
[e]Calcification score: 0 (no calcium deposits); 1 (a few calcified deposits); 2 (multiple deposits); 3 (band of calcification throughout entire section).
[f]Number affected/number examined (% incidence).
*Significantly different from the referent group at $p < 0.05$, based on analyses performed by the study authors.
ǂThe distribution of histological scores was significantly different from the reference group at $p < 0.05$, based on analyses performed by the study authors.

Ca = calcium; SP = monosodium phosphate; P = phosphorus; SD = standard deviation; NZW = New Zealand White

Table B-7. Significant Effects in Male Wistar Rats Administered Inorganic Phosphate (as KH_2PO_4) in the Diet for 4 Weeks[a]

Effects (units)	Dose in mg P/kg-d (% P in diet)				
	250 (0.3% P in diet; referent)	**450 (0.6% P in diet)**	**670 (0.9% P in diet)**	**920 (1.2% P in diet)**	**1,000 (1.5% P in diet)**
Body-weight gain (g/4 wk)	95 ± 5.1[b]	82.3 ± 0.9 (−13%)[c]	73.3 ± 4.4** (−23%)[c]	84.0 ± 4.4 (−12%)[c]	58.7 ± 6.0** (−38%)[c]
Body-weight gain/100 g intake	18.78 ± 1.24	18.21 ± 0.48 (−3%)	16.21 ± 0.63 (−14%)	18.01 ± 1.14 (−4%)	13.88 ± 1.3* (−26%)
Intake (g/4 wk)	507.9 ± 13.9	453.8 ± 15.6* (−11%)	451.1 ± 13.4* (−11%)	467.0 ± 7.1* (−8%)	421.4 ± 4.6** (−17%)
P balance					
Fecal (mg/d)	23.8 ± 2.9	30.6 ± 3.7 (+29%)	32.4 ± 2.3* (+36%)	45.2 ± 6.2* (+90%)	47.5 ± 3.9** (+100%)
Urinary (mg/d)	4.2 ± 0.4	56.5 ± 5.8** (+1,245%)	102.1 ± 9.0** (+2,331%)	179.4 ± 0.1** (+4,171%)	274.9 ± 15.6** (+6,445%)
Net absorption (mg/d)	28.0 ± 2.2	60.2 ± 4.8** (+115%)	99.0 ± 6.8** (+254%)	137.6 ± 7.1** (+391%)	150.1 ± 12.3** (+436%)
Balance (mg/d)	23.8 ± 2.3	3.7 ± 5.0** (−4%)	−3.1 ± 12.1 (−113%)	−41.9 ± 7.1** (−276%)	−124.8 ± 21.3** (−624%)
Ca balance					
Urinary (mg/d)	0.53 ± 0.04	0.23 ± 0.02** (−57%)	0.17 ± 0.01** (−68%)	0.10 ± 0.00** (−81%)	0.09 ± 0.02** (−83%)
Net absorption (mg/d)	34.9 ± 5.7	31.5 ± 7.1 (−10%)	28.7 ± 7.4 (−18%)	23.3 ± 8.5 (−33%)	4.7 ± 6.6** (−87%)
Balance (mg/d)	34.3 ± 5.7	31.3 ± 7.1 (−9%)	28.5 ± 7.4 (−17%)	23.2 ± 8.5 (−32%)	4.7 ± 6.6** (−86%)
Serum chemistry					
PTH (pg/mL)	7.82 ± 3.81	33.76 ± 11.43 (+332%)	32.53 ± 19.48 (+316%)	25.06 ± 10.35 (+220%)	75.12 ± 0.28** (+861%)
$1,25(OH)_2D_3$ (pg/mL)	65.4 ± 4.7	102.6 ± 25.9 (+57%)	115.8 ± 12.4** (+77%)	124.9 ± 51.4 (+91%)	112.3 ± 19.0 (+72%)

[a]Tani et al. (2007).
[b]Mean ± SEM for $n = 6$ per group.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from the referent group at $p < 0.05$, based on analyses performed by the study authors.
**$p < 0.01$.

$1,25(OH)_2D3$ = 1,25-dihydroxy-vitamin D_3; Ca = calcium; KH_2PO_4 = monopotassium phosphate; P = phosphorus; PTH = parathyroid hormone; SEM = standard error of the mean.

Table B-8. Significant Effects in Male Sprague Dawley Rats Administered Inorganic Phosphate (as KH_2PO_4) in the Diet for 4 Weeks[a]

Parameter (units)	Dose in mg P/kg-d (% P in diet)	
	530 (0.6% P in diet; referent)	1,100 (1.2% P in diet)
Body weight (g)	352 ± 7.5[b]	345 ± 8.0 (−2%) [c]
NEFA (mEq/L)	0.47 ± 0.03	0.34 ± 0.02* (−28%)
PTH (pg/mL)	40 ± 12.6	256.4 ± 75.7* (+541%)
FGF-23 (pg/mL)	231 ± 47.6	408 ± 82.6 (+77%)
BUN (mg/dL)	12.8 ± 0.5	16.9 ± 1.6* (+32%)

[a]Abuduli et al. (2016).
[b]Mean ± SE for six animals/group.
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from referent group at $p < 0.05$ based on analyses performed by the study authors.

BUN = blood urea nitrogen; FGF-23 = fibroblast growth factor-23; KH_2PO_4 = monopotassium phosphate; NEFA = nonesterified fatty acids; P = phosphorus; PTH = parathyroid hormone; SE = standard error.

Table B-9. Significant Effects in Birmingham-Wistar Rats Administered Inorganic Phosphate as $Na_4P_2O_7$ or Na_2HPO_4 in the Diet for 16 Weeks[a]

Parameter (units)	Percent in Diet				
	0.5% (referent)	**1% (as $Na_4P_2O_7$)**	**2.5% (as $Na_4P_2O_7$)**	**5% (as $Na_4P_2O_7$)**	**5% (as Na_2HPO_4)**
Males					
Dose (mg P/kg-d)[b]	**280**	**396 (estimated)**	**570 (estimated)**	**860**	**840**
Body-weight gain (g)	210 ± 20[c]	245 ± 16 (+17%)[d]	229 ± 15 (+9%)[d]	187 ± 15 (−11%)[d]	234 ± 14 (+11%)[d]
Food consumption (g)	1,309 ± 28	1,359 ± 27 (+4%)	1,305 ± 24 (+0%)	1,213 ± 48 (−7%)	1,363 ± 18 (+4%)
RBCs (millions/mm^3)	7.51 ± 0.20	7.95 ± 0.25 (+6%)	7.75 ± 0.17 (+3%)	7.67 ± 0.18 (+2%)	8.25 ± 0.31 (+10%)
Hb (g/100 mL)	13.1 ± 0.17	12.8 ± 0.24 (−2%)	12.4 ± 0.21* (−5%)	12.5 ± 0.25 (−5%)	13.9 ± 0.29* (+6%)
Specific gravity	1.06 ± 0.003	1.05 ± 0.005 (−1%)	1.04 ± 0.006* (−2%)	1.04 ± 0.005* (−2%)	1.05 ± 0.002** (−1%)
Relative organ weights (mg/100 g live weight)					
Heart	244 ± 4	255 ± 6 (+5%)	251 ± 77 (+3%)	295 ± 19* (+21%)	256 ± 7 (+5%)
Stomach	378 ± 12	365 ± 15 (−3%)	388 ± 12 (+3%)	608 ± 39** (+61%)	407 ± 14 (+8%)
Intestines	2,229 ± 112	2,108 ± 111 (−5%)	1,964 ± 83 (−12%)	2,716 ± 239 (+22%)	1,940 ± 99 (−13%)
Kidneys	634 ± 21	598 ± 17 (−6%)	648 ± 24 (+2%)	769 ± 34* (+21%)	741 ± 15** (+17%)
Testes	962 ± 42	900 ± 29 (−6%)	905 ± 42 (−6%)	1,233 ± 79* (+28%)	1,005 ± 37 (+4%)
Gross pathology					
Pale, pitted; kidneys	0/10[d] (0%)[d]	0/10[d] (0%)[d]	0/10[d] (0%)[d]	6/10[e, f] (60%)[d]	6/10[e, f] (60%)[d]
Calcification; kidneys	0/10 (0%)	0/10 (0%)	0/10 (0%)	5/10[f] (50%)	6/10[f] (60%)
Hypertrophy; stomach	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)	0/10 (0%)
Kidney concentration test					
Males	1.0622 ± 0.0026	1.0547 ± 0.0047	1.0429 ± 0.0061*	1.0432 ± 0.0051*	1.0488 ± 0.0018**
Females					
Dose (mg P/kg-d)[b]	**350**	**500 (estimated)**	**725 (estimated)**	**1,100**	**1,000**
Body-weight gain (g)	137 ± 7	129 ± 6 (−6%)	129 ± 7 (−6%)	114 ± 7* (−17%)	140 ± 8 (+2%)
Food consumption (g)	1,184 ± 28	1,110 ± 28 (−6%)	1,116 ± 16 (−6%)	1,055 ± 26 (−11%)	1,168 ± 23 (−1%)
RBCs (millions/mm^3)	7.30 ± 0.18	7.21 ± 0.15 (−1%)	7.00 ± 0.19 (−4%)	6.91 ± 0.53 (−5%)	7.92 ± 0.13* (+8%)

Table B-9. Significant Effects in Birmingham-Wistar Rats Administered Inorganic Phosphate as $Na_4P_2O_7$ or Na_2HPO_4 in the Diet for 16 Weeks[a]

Parameter (units)	Percent in Diet				
	0.5% (referent)	**1% (as $Na_4P_2O_7$)**	**2.5% (as $Na_4P_2O_7$)**	**5% (as $Na_4P_2O_7$)**	**5% (as Na_2HPO_4)**
Hb (g/100 mL)	12.4 ± 0.51	12.0 ± 0.46 (−3%)	12.9 ± 0.23 (+4%)	12.1 ± 0.36 (−2%)	13.2 ± 0.54* (+6%)
Specific gravity	1.06 ± 0.002	1.06 ± 0.003 (0%)	1.06 ± 0.002 (0%)	1.04 ± 0.001** (−1%)	1.05 ± 0.003* (−1%)
Relative organ weights (mg/100 g live weight)					
Heart	278 ± 4	273 ± 5 (−2%)	295 ± 10 (+6%)	311 ± 9* (+12%)	285 ± 9 (+3%)
Stomach	451 ± 16	459 ± 15 (+2%)	506 ± 22 (+12%)	721 ± 63** (+60%)	486 ± 23 (+8%)
Intestines	2,521 ± 73	2,928 ± 149 (+16%)	2,626 ± 85 (+4%)	3,203 ± 149** (+27%)	2,696 ± 103 (+7%)
Kidneys	601 ± 12	629 ± 21 (+5%)	743 ± 24** (+24%)	893 ± 42** (+49%)	838 ± 35** (+39%)
Gross pathology					
Pale, pitted; kidneys	0/10 (0%)	0/10 (0%)	2/10 (20%)	5/10[f] (50%)	7/10[f] (70%)
Calcification; kidneys	0/10 (0%)	0/10 (0%)	2/10 (20%)	5/10[f] (50%)	5/10[f] (50%)
Hypertrophy; stomach	0/10 (0%)	0/10 (0%)	3/10 (30%)	6/10[f] (60%)	0/10 (0%)
Kidney concentration test					
Females	1.0592 ± 0.0024	1.0628 ± 0.0026	1.0561 ± 0.0015	1.0445 ± 0.0014**	1.0513 ± 0.0025*
Combined sexes					
P excretion; 3 wk (%)	11.4 ± 0.18	NR	NR	82.5 ± 3.12[f] (+71%)	NR
P excretion; 8 wk (%)	NR	NR	NR	74.2 ± 3.03	75.2 ± 0.93
Histopathology					
Renal damage	5/20 (25%)	19/20[f] (95%)	20/20 (100%)	20/20[f] (100%)	20/2 (100%)
Cortical atrophy	3/20 (15%)	12/20[f] (60%)	12/20[f] (60%)	3/20 (15%)	3/20 (15%)
Cortical hyaline degeneration	2/20 (10%)	11/20[f] (55%)	11/20[f] (55%)	4/20 (20%)	2/20 (10%)
Medullary calcification	0/20 (0%)	1/20 (5%)	6/20[f] (30%)	14/20[f] (70%)	15/20[f] (75%)
Medullary necrosis	0/20 (0%)	1/20 (5%)	2/20 (10%)	12/20[f] (60%)	13/20[f] (65%)
Tubular casts	1/20 (5%)	0/20 (0%)	6/20 (30%)	11/20[f] (55%)	11/20[f] (55%)
Hemorrhages and exudate	1/20 (5%)	9/20[f] (45%)	10/20[f] (50%)	12/20[f] (60%)	12/20[f] (60%)

Table B-9. Significant Effects in Birmingham-Wistar Rats Administered Inorganic Phosphate as $Na_4P_2O_7$ or Na_2HPO_4 in the Diet for 16 Weeks[a]

Parameter (units)	Percent in Diet				
	0.5% (referent)	1% (as $Na_4P_2O_7$)	2.5% (as $Na_4P_2O_7$)	5% (as $Na_4P_2O_7$)	5% (as Na_2HPO_4)
Chronic inflammatory changes	0/20 (0%)	0/20 (0%)	1/20 (5%)	14/20[f] (70%)	14/20[f] (70%)

[a]Datta et al. (1962).
[b]P content of the diet was not reported by Datta et al. (1962) for the 1 and 2.5% dose groups for either males or females. However, doses can be reasonably estimated in units of mg P/kg-day for these groups. For males, the inclusion of $Na_4P_2O_7$ in the diet at 5% (860 mg P/kg-day) corresponds to an increase of 580 mg P/kg-day above the referent dose (0.5%, 280 mg P/kg-day). Assuming linearity, this amount was scaled for the 1 and 2.5% dose groups (116 and 290 mg P/kg-day, respectively) and added to the referent dose to generate reasonably estimated doses in units of mg P/kg-day. Thus, the inclusion of $Na_4P_2O_7$ in the diet at 1 and 2.5% correspond to estimated doses of 396 and 570 mg P/kg-day, respectively, in males. For females, the inclusion of $Na_4P_2O_7$ in the diet at 5% (1,100 mg P/kg-d) corresponds to an increase of 750 mg P/kg-day above the referent dose (0.5%, 350 mg P/kg-day). Assuming linearity, this amount was scaled for the 1 and 2.5% dose groups (150 and 375 mg P/kg-day, respectively) and added to the referent dose to generate reasonably estimated doses in units of mg P/kg-day. Thus, the inclusion of $Na_4P_2O_7$ in the diet at 1 and 2.5% correspond to estimated doses of 500 and 725 mg P/kg-day, respectively, in females.
[c]Mean ± SE.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
[e]Number affected/number examined (% incidence).
[f]Significantly different from referent group at $p < 0.05$, based on two-sided *t*-test (continuous data) or Fisher's exact test (incidence data) performed for this review
*Significantly different from referent group at $p < 0.05$, based on analyses performed by the study authors.
**$p < 0.01$.

Hb = hemoglobin; Na_2HPO_4 = disodium phosphate; $Na_4P_2O_7$ = sodium pyrophosphate; NR = not reported; P = phosphorus; RBC = red blood cell; SE = standard error.

Table B-10. Significant Effects in Male Wistar Rats Administered Inorganic Phosphate (as K_2HPO_4 or $[NaPO_3]_6$) in the Diet for 150 Days[a]

Parameter (units)	Dose in mg P/kg-d (% P in diet)			
	380 (0.43% P in diet as K_2HPO_4 referent)	**1,100 (1.3% P in diet as K_2HPO_4)**	**400 (0.46% P in diet as $[NaPO_3]_6$; referent)**	**1,100 (1.2% P in diet as $[NaPO_3]_6$)**
Body-weight gain (g)	385 ± 11[b]	432 ± 9** (+12%)[c]	403 ± 9[b]	376 ± 9 (−7%)[c]
Relative kidney weight (g/100 g body weight)	0.71 ± 0.03	0.73 ± 0.04 (+3%)	0.68 ± 0.03	0.73 ± 0.04 (+7%)
Relative testes weight (g/100 g body weight)	0.79 ± 0.03	0.75 ± 0.19 (−5%)	0.72 ± 0.02	0.80 ± 0.01** (+11%)

[a]Dymsza et al. (1959).
[b]Mean ± measure of variance (not specified).
[c]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significant difference between groups administered the same compound (high K_2HPO_4 vs. low K_2HPO_4 or high $[NaPO_3]_6$ vs. low $[NaPO_3]_6$) at $p \leq 0.05$, based on analyses performed by the study authors.
**$p \leq 0.01$.

K_2HPO_4 = dipotassium phosphate; $[NaPO_3]_6$ = sodium hexametaphosphate; P = phosphorus.

APPENDIX C. REFERENCES

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