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Provisional Peer Reviewed Toxicity Values for

Phosphorus pentoxide
(CASRN 1314-56-3)

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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PHOSPHORUS PENTOXIDE (CASRN 1314-56-3)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS; U.S. EPA, 2007) does not list a chronic RfD, chronic RfC or cancer assessment for phosphorus pentoxide. Subchronic or chronic RfDs, RfCs or cancer assessments for phosphorus pentoxide are not listed in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) does not include phosphorus pentoxide. No standards for occupational exposure to phosphorus pentoxide have been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the National Institute for Occupational Safety and Health (NIOSH, 2007) or the Occupational Safety and Health Administration (OSHA, 2007). The Agency for Toxic Substances and Disease Registry (ATSDR, 2007), the International Agency for Research on Cancer (IARC, 2007), and the World Health Organization (WHO, 2007) have not published toxicological reviews on phosphorus pentoxide. A toxicity review on inorganic phosphorus compounds that included phosphorus pentoxide, was consulted for relevant information (U.S. EPA, 1989).

Literature searches for studies relevant to the derivation of provisional toxicity values for phosphorus pentoxide (CASRN 1314-56-3) were conducted in MEDLINE, TOXLINE special, and DART/ETIC (1960's - July 2007); BIOSIS (August 2000 - July 2007); TSCATS/TSCATS 2, CCRIS, GENETOX, HSDB, and RTECS (not date limited); and Current Contents (February 2007 - July 2007).

Due to its high affinity for water, phosphorus pentoxide is used as drying agent. It is also used in the manufacture of other chemicals and surfactants as a catalyst in air blowing of asphalt and in other applications (U.S. EPA, 1989). Phosphorus pentoxide dissolves in water with great liberation of heat, forming metaphosphoric acid (HPO_3) and then phosphoric acid (H_3PO_4). The empirical formula for phosphorus pentoxide is P_4O_{10}.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

REVIEW OF PERTINENT LITERATURE

Human Studies

The only information available regarding human exposure to phosphorus pentoxide is that from an occupational study conducted by Dutton et al. (1993). The investigators studied lung function in workers exposed to phosphorus pentoxide, phosphoric acid, fluorides and coal tar pitch volatiles while refining phosphorus rock to obtain elemental phosphorus. Maximum air levels measured in the study were 2.23 mg/m^3 phosphorus pentoxide, 4.21 mg/m^3 fluorides and 1.04 mg/m^3 coal tar pitch volatiles; levels of phosphoric acid were not provided. No additional information regarding exposure levels was reported and sampling and analytical methods were not discussed. All 131 employees of the refinery underwent annual pulmonary function testing (4-8 annual determinations). Estimated years of exposure in work area where respiratory irritant levels exceeded "recommended levels" were used as the exposure index. The years of exposure ranged from less than 5 to more than 20, with substantial numbers of workers at the higher durations. The recommended levels were 1 mg/m^3 for phosphorus pentoxide, 2.5 mg/m^3 for fluorides and 0.2 mg/m^3 for coal tar pitch volatiles. Regression analyses of individual mean values for percent predicted pulmonary function against years of exposure revealed no statistically significant reductions in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and forced exploratory flow rate from 25% to 75% of FVC (FEF_{25-75}) for nonsmokers or former smokers. In smokers, although statistically significant reductions occurred in all three parameters, these disappeared when adjustment for the effect of smoking was made. No conclusions regarding phosphorus pentoxide can be drawn from this study.

Animal Studies

No information was located regarding the effects of phosphorus pentoxide in animals following oral exposure. The only data regarding inhalation exposure to phosphorus pentoxide are acute toxicity data provided by Ballantyne (1981) in an abstract. The investigator exposed adult male rats, rabbits, mice and guinea pigs for 1 hour to phosphorus pentoxide smoke (36-2130 mg/m^3), generated by burning red phosphorus in an air stream, followed by a 14-day observation period. The respective 1-hour LC_{50} values were 1217, 1689, 271 and 61 mg/m^3. Most deaths occurred during or within 24 hours of exposure. In all species, the respiratory tract was the target of toxicity. Ballantyne (1981) stated that concentrations (in mg/m^3) of phosphorus

pentoxide not associated with respiratory tract pathology in 14-day survivors were 450 in rats and rabbits, 111 in mice and <36 in guinea pigs.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL p-RfD VALUES FOR PHOSPHORUS PENTOXIDE

There are no oral data for phosphorus pentoxide. White phosphorus smoke, which is used as a screening smoke by the military, contains phosphorus pentoxide as a major constituent. There is an RfD for white phosphorus on IRIS (U.S. EPA, 1993). Therefore, white phosphorus was considered as a potential surrogate for derivation of the RfD. The RfD for white phosphorus on IRIS is based on critical effects of parturition mortality and forelimb hair loss in a one-generation reproduction study in rats (Condray, 1985). Little is known regarding the pharmacokinetics and mechanism of action of orally administered white phosphorus, but the available data suggest that some of the effects may be due to white phosphorus itself, and that white phosphorus may be transformed not only to phosphoric acid, but also to phosphine in the body (ATSDR, 1997). Phosphorus pentoxide would not be expected to undergo transformation to phosphine in the body. In addition, some of the characteristic effects of white phosphorus exposure by the inhalation, oral and dermal routes have not been seen in the studies of white phosphorus smoke, the mixture that contains phosphorus pentoxide. These effects include the critical effects on which the RfD is based (parturition mortality and forelimb hair loss), fatty degeneration of the liver, phossy jaw in humans and a particular pattern of bone effects in developing humans and animals (ATSDR, 1997; U.S. EPA, 1989, 1993). Accordingly, derivation of an RfD for phosphorus pentoxide by analogy to white phosphorus is not recommended.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR PHOSPHORUS PENTOXIDE

The inhalation data available for phosphorus pentoxide are limited to an occupational study of workers exposed to phosphorus pentoxide, phosphoric acid, fluorides and coal tar pitch volatiles (Dutton et al., 1993). Pulmonary function tests conducted on the workers several times a year did not reveal any significant alterations. There is also information on acute lethal concentrations in four animal species presented in abstract form (Ballantyne, 1981). This information is inadequate for RfC derivation.

Because the major environmental transformation of phosphorus pentoxide is by hydrolysis to phosphoric acid, and an RfC for phosphoric acid is available on IRIS, we explored the possibility of using phosphoric acid as a surrogate chemical for derivation of the RfC. Phosphorus pentoxide is an extremely hygroscopic substance that is used as a drying agent. Phosphorus pentoxide reacts readily with water to form phosphoric acid. The reaction with water is exothermic releasing 70,000 calories (Bayer, 1954). Phosphorus pentoxide will even extract the elements of water from many other substances themselves considered good dehydrating agents (i.e., it converts pure HNO_3 into N_2O_5 and H_2SO_4 into SO_3) (Cotton et al., 1999). The Dutton occupational study suggests that the pentoxide was measured in the

workplace air. Therefore, we cannot conclude that the inhalation exposure was only the hydrolysis product, phosphoric acid. In addition, we have no conclusive evidence of complete and immediate hydrolysis. Due to the highly exothermic nature of the hydrolysis process, at least part of the toxicity can be a result of this process occurring in the lung. Therefore, we have no basis for using phosphoric acid as a surrogate for phosphorous pentoxide. Lacking other relevant studies, development of inhalation toxicity values is precluded.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PHOSPHORUS PENTOXIDE

Weight-of-Evidence Descriptor

There are no data with which to assess the potential carcinogenicity of phosphorus pentoxide. Under the 2005 Guidelines for Carcinogen Assessment (U.S. EPA, 2005), there is *inadequate information to assess the carcinogenic potential* of phosphorus pentoxide.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for phosphorus pentoxide is precluded by the lack of suitable data.

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