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Provisional Peer Reviewed Toxicity Values for
Triphenylphosphine oxide
(CASRN 791-28-6)

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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
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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 TRIPHENYLPHOSPHINE OXIDE (CASRN 791-28-6)

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

RfD, RfC, and, cancer assessments are not available on IRIS (U.S. EPA, 2007) or in HEAST (U.S. EPA, 1997) for triphenylphosphine oxide (TPPO). ACGIH (1996), OSHA (2001), and NIOSH (1997) have not established occupational exposure limits to protect workers exposed to TPPO. No documents on TPPO were listed in the CARA database (U.S. EPA, 1994).

TPPO has not been the subject of toxicological reviews by ATSDR (2001), NTP (2001) or WHO (2001). Literature searches of HSDB, RTECS, TSCATS, MEDLINE, and TOXLINE (and its subfiles) databases were conducted and screened in January 1998. Updated literature searches of TOXLINE, CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS were conducted in September 2001 for literature from 1998-2001 and again in January 2007. Additional toxicology data were not found in any of these searches. 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 Data

No studies of the effects of TPPO on humans were found.

Animal Data

A small number of unpublished reports of the toxic effects of TPPO on laboratory animals were found in the TSCATS subfile of TOXLINE. These studies are characterized by a low number of experimental animals, an acute exposure regimen (maximum of 21 days), and a limited range of doses.

Beagle dogs (2/sex/group) were administered a single oral dose of either 300 or 500 mg/kg in corn oil (Atochem, 1992). All dogs died, preceded by violent convulsions, tremors, uncoordinated body movements, "paddling" and "swimming" movements, aggressive behavior, vocalization, excessive salivation, dyspnea, and emesis. Neurological examination of four dogs that were still alive on the day of dosing showed evidence of impaired visual placing, locomotion, standing, and righting reflexes. However, flexor and extensor reflexes were unaffected in three of the four dogs.

Because of the deaths of the dogs receiving doses of 300 or 500 mg/kg, a subsequent groups with two dogs each received single doses of either 50 mg/kg (2 females; 2 week observation period) or 100 mg/kg (1 male and 1 female; 1 week observation period) TPPO (Atochem, 1992). Plasma cholinesterase activity was measured pretest and 3 hours after the last dose. Brain cholinesterase was measured after sacrifice. The two dogs receiving 50 mg/kg TPPO showed no unusual signs after dosing or during the 2-week observation period. The two dogs receiving 100 mg/kg showed similar symptoms to those that had received 300 or 500 mg/kg, but recovered by the next day and showed no unusual signs during the 1-week observation period. No impairment of reflexes was noted during the observation period for dogs receiving either 50 or 100 mg/kg. Slight body weight losses occurred only in dogs receiving 50 mg/kg. Cholinesterase activity measurements showed no clear evidence of inhibition in either dose group. Neurological examination of the dogs receiving single doses of either 50 or 100 mg/kg showed no evidence of impaired reflexes during the observation period.

A subsequent 7-week neurotoxicity study was conducted with exposure of six beagle dogs (3/sex) receiving either 0 or 50 mg/kg-day TPPO in corn oil for 21 days. Persistence and reversibility of effects were evaluated in a subsequent 4-week observation period (Atochem, 1992; Biodynamics, Inc., 1979). The TPPO was administered orally in corn oil. Neurological examinations were performed on days 0, 1, 4, 7, 10, 21, 28, 35, 42, and 49. Five of the six dogs receiving TPPO (2 male and 3 female) exhibited violent convulsions, tremors, uncoordinated body movements, "paddling" and "swimming" movements, excessive salivation, vocalization, and dyspnea following the first dose. Signs appeared approximately 1-2 hours after dosing and subsided within 4 hours after dosing. Three female dogs exhibited slight intermittent head tremors following the second dose. No further signs indicative of neurologic effects were seen for the duration of the experiment, with one exception. One male dog choked immediately after

dosing on two occasions (days 4 and 17). The dog became rigid and exhibited convulsions, tremors, dyspnea, excessive salivation, and inability to stand. This was followed by rapid recovery, and the dog appeared normal within 30 minutes. This effect seemed to be associated with partial aspiration of the dosing mixture. There were no signs of neurologic effects during any of the examinations throughout the experiment. Weight gains of males receiving TPPO were equal to or greater than the controls. Two females receiving TPPO showed slight weight losses during the first weeks of the study; however, weight gains during the recovery period were considered comparable to controls. There was no evidence of cholinesterase inhibition in plasma or brain tissue from dogs treated with TPPO. Gross pathology examinations did not indicate any findings related to TPPO exposure. The results indicated 50 mg/kg-day as the minimal effective dose without changes in cholinesterase activity levels in the brain or plasma.

Four dogs (2/sex/group) were exposed to mean concentrations of 10.5 or 78.5 mg/m³ for 6 hours/day, 5 days/week, for 4 weeks (Rohm & Haas Company, 1992). A control group was exposed to isopropanol for the same period. After the exposure period, the animals were observed for 4 weeks and then sacrificed. There were no signs of neurological or other effects during or after the exposure. No gross lesions or abnormalities were observed during the experiment.

In an acute lethality experiment in hens, the oral LD₅₀ was found to be greater than 5.0 g/kg TPPO (Rohm & Haas Company, 1992). No indication of permanent locomotor impairment was noted after doses of 3.5 or 5.0 g/kg. At 7.2 g/kg, moderate locomotor impairment was noted on day 14 in 5 of 9 subjects, though this may represent a general toxic response rather than a specific neurotoxic effect.

Non-availability of Relevant Studies To fulfill the reporting requirements of TSCA, BASF Corporation (1992) reported that acute and subchronic tests for TPPO had been conducted for durations ranging from single doses up to 3 months. The details of these studies, however, were not included in the submission letter, and no attached reports were included in the TSCATS file. The letter states that an English translation of a summary of the studies indicates that neurotoxicity was observed in several species following administration of TPPO by several routes of exposure. Liver effects were also mentioned for rats and dogs in the subchronic feeding studies. The full text of these studies was not obtained from BASF Corporation.

Immunotoxicity TPPO has been shown to suppress immune responses *in vitro* (Esa et al., 1988; Fautz and Miltenburger, 1994). Esa et al. (1988) evaluated several organophosphorous compounds for their effects on human *in vitro* cell-mediated responses. At a non-cytotoxic concentration of 5 µM TPPO caused significant suppression of antigen-specific lymphocyte proliferation (p<0.01). Also, TPPO caused a significant inhibition of monocyte antigen presentation at concentrations as low as 1 µM (p<0.001).

Fautz and Miltenburger (1994) investigated the effects of TPPO on different immune functions *in vitro* using peritoneal cells and splenocytes isolated from female C57B1 mice. A concentration-related suppression of spleen cell natural killer cell activity was observed after treatment with 33.3 µM TPPO for 1 hour. TPPO, however, had no significant effect on macrophage phagocytotic activity, blastogenesis (T and B lymphocytes), and antibody synthesis

(B lymphocytes). In summary, TPPO was found to be an immunomodulating agent that elicited adverse effects on the cells of the innate immunity system, but was inactive against adaptive immunity functions of the T- and B-lymphocytes.

Related Compounds The compound triphenylphosphine (TPP) was also studied in parallel experimental protocols to those for TPPO in several of the reports examined. For example, four beagle dogs (2/sex) receiving a single oral dose of 500 mg/day exhibited convulsions, tremors, and other signs as described for TPPO (Atochem, 1992). The dogs were lethargic on the following day, but all survived and had recovered by day 4. Minimal signs of neurological damage were noted by the end of a 4-week observation period. Another group of six beagle dogs (3/sex) received a single dose of 300 mg/kg of TPP, followed by doses of 50 mg/kg-day for the following 13 days. The dogs exhibited convulsions, tremors, and other signs as described for TPPO. One of the six dogs was found dead the day after initial dosing, and the other dogs were lethargic or recumbent. The dogs initially recovered after the single 300 mg/kg dose; however, on days 13 and 14 these dogs exhibited front and hind leg weakness with inability to stand for normal periods. These signs persisted during the 2-week observation period. Impairment of the flexor, extensor, and visual placing reflexes was observed on days 14, 21, and/or 28. There was no indication of inhibition of cholinesterase activity in blood or brain samples in either group.

In a subsequent 7-week oral exposure study, groups of 6 beagle dogs (3/sex) were administered TPP doses of 25 mg/kg-day for 21 consecutive days, followed by a 4-week observation period (Atochem, 1992). Controls received only the corn oil vehicle. All animals survived for the duration of the experiment. Signs of neurological impairment, ataxia and hindlimb weakness, were first noted after 14 days in 3 of 6 dogs. There was an initial slight improvement immediately after the end of the exposure period; however, there was no further improvement. Histopathological examination showed myelin degeneration in the spinal cord of dosed animals. Similar lesions were noted to a lesser extent in the cerebrum. Peripheral nerves were not affected.

In an inhalation study, groups of four beagle dogs were exposed to concentrations of either 18.0 or 94.8 mg/m³ of TPP for 6 hours/day, 5 days/week for 5 weeks (Atochem, 1992). Control groups received 150 mg/m³ of the xylene vehicle. Following the end of the exposure, the dogs were observed during a 4-week recovery period. Visual evidence of locomotor dysfunctions was seen in the high-dose group in the second week of exposure. These signs persisted for the remainder of the exposure period and throughout the recovery period; however, the signs did not increase in severity. Levels of serum alkaline phosphatase and cholesterol were elevated in both exposure groups during the exposure period, but there was some evidence of recovery during the observation period. Patchy to segmental degeneration of the myelin in the white tracts of the brain and spinal cord were seen in both exposure groups.

In a subsequent inhalation study, groups of two beagle dogs (1/sex/group) were exposed to concentrations of 0.5, 3.2, 9.7, or 28 mg/m³ TPP as a respirable aerosol in a xylene vehicle for 6 hours/day, 5 days/week, for 4 weeks (Atochem, 1992). Controls received the xylene vehicle only at 150 ppm. Another set of beagle dogs (1/sex/group) were exposed to concentrations of 0.3, 3.6, or 24 mg/m³ TPP for 6 hours for 2 days, and then observed during a 4-week recovery

period. All animals survived for the duration of the experiments. Signs of neurological impairment were noted in male dogs exposed to 24 mg/m³ for 2 days and in males and females exposed to 28 mg/m³ for 4 weeks. Histopathological examinations showed moderate generalized vacuolative degeneration of the spinal cord in dogs exposed to 28 mg/m³ for 4 weeks. Similar spinal cord lesions, although minimal and focal in nature, were also observed in dogs in the 0.5 and 3.2 mg/m³ dose groups exposed for 4 weeks. These lesions were not observed in control dogs.

DERIVATION OF A PROVISIONAL SUBCHRONIC AND CHRONIC RfD FOR TRIPHENYLPHOSPHINE OXIDE (TPPO)

The studies reported in the initial submission from Atochem (1992) indicate that TPPO administered as a single dose over a long duration can induce dramatic neurological effects. Considering the clinical symptoms, brain/plasma cholinesterase activity levels and neurological examinations, the 7-week dog study (Atochem, 1992; Biodynamics, Inc., 1979) is adequate to develop a subchronic p-RfD.

The Atochem (1992); Biodynamics, Inc. (1979) study reported clinical symptoms of cholinesterase inhibition without any histopathological changes or plasma/brain cholinesterase activity levels in dogs. Thus, the 50 mg/kg-day dose of TPPO is considered a minimum effect level.

LOAEL (minimal)	=	50 mg/kg-day
Uncertainty Factor	=	3000 (3* for use of a minimal LOAEL in place of a NOAEL, 10 for use of animal studies rather than human studies, 10 for sensitive human subgroups, 3 for lack of developmental and reproductive studies, and 3 for lack of additional supporting studies)
subchronic p-RfD	=	LOAEL / Uncertainty Factor
	=	50 mg/kg-day / 3000
subchronic p-RfD	=	0.02 mg/kg-day or 2E-2 mg/kg-day

* Half-log of 10 rounded to 3

Although there is a lack of chronic animal or human studies, the studies used for derivation of the provisional subchronic RfD (Atochem, 1992; Biodynamics, 1979) are considered appropriate for use in deriving the chronic provisional RfD. No additional Uncertainty Factor for subchronic-to-chronic extrapolation is applied because the adverse effects mediated by inhibition of cholinesterase are considered to be short lived and reversible at low doses. Thus, doses producing effects following a repeated daily exposure regimen are comparable to those following a single dose. Also, comparable degrees of cholinesterase

inhibition are seen from the same dose, whether delivered in one acute dose or following subchronic or chronic dosing. Additional justification is provided in the IRIS file on Aldicarb, Section I.A.3. (U.S. EPA, 2007) and Rhone-Poulenc (1992).

$$\text{p-RfD} = 0.02 \text{ mg/kg-day or } 2\text{E-}2 \text{ mg/kg-day}$$

Due to lack of complete published information and additional studies, low confidence in the provisional subchronic and chronic RfDs and data base is recommended.

DERIVATION OF A PROVISIONAL CHRONIC RfC FOR TRIPHENYLPHOSPHINE OXIDE (TPPO)

There is insufficient information available to derive a p-RfC for TPPO. The single inhalation study reviewed for this risk issue paper was inadequate for a p-RfC derivation. The study included 2 dogs/sex/group with no neurological or other effects noted during or after the exposure.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR TRIPHENYLPHOSPHINE OXIDE (TPPO)

The potential human carcinogenicity hazard for TPPO cannot be determined due to an inadequate database (U.S. EPA, 2005). With one exception, the toxicity studies reviewed for this risk issue paper were acute studies with a maximum exposure duration of 21 days. The TSCA initial submission from BASF (1992) briefly indicated that liver effects in rats and dogs had been observed in a subchronic feeding study, however, the nature of the effects and details of the experimental protocol were not provided. The available database is inadequate to determine the potential human carcinogenicity hazard for TPPO. Under the final guidelines (U.S. EPA, 2005) the *data are inadequate for assessment of human carcinogenic potential*.

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