09-10-02

Provisional Peer Reviewed Toxicity Values for

Tris(2-ethylhexyl)phosphate
(CASRN 78-42-2)

Derivation of a Chronic Oral RfD

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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

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Derivation of a Chronic Oral RfD

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

No chronic RfD for tris(2-ethylhexyl)phosphate is available on IRIS (U.S. EPA, 2001) or in the HEAST (U.S. EPA, 1997) or Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). No documents for tris(2-ethylhexyl)phosphate are included on the CARA list (U.S. EPA, 1991, 1994). ATSDR (2001) and IARC (2001) have not reviewed the toxicity of tris(2-ethylhexyl)phosphate. The NTP (2001) status report, an Environmental Health Criteria document on flame retardants (IPCS, 2000) and a review of esters of organic phosphorous (Bisei, 2001) were consulted for information. Computer literature searches of TOXLINE (from 1981), HSDB, RTECS and TSCATS had been performed in 1992 and updated in April, 1994. Updated literature searches (1994 - 2001) of TOXLINE, MEDLINE, CANCERLIT, EMIC/EMICBACK, DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September, 2001.

REVIEW OF PERTINENT LITERATURE

In range-finding studies, groups of 5 male and 5 female Fischer 344/N rats (initially approximately 6 weeks of age) and groups of 5 male and 5 female B6C3F1 mice (initially approximately 8 weeks of age) were treated by gavage with 0, 375, 750, 1500, 3000, or 6000 mg/kg-day of tris(2-ethylhexyl)phosphate (purity 97-99%) in corn oil for 14 consecutive days (NTP, 1984). Parameters used to assess toxicity were mortality, body weight gain, and gross necropsy of major tissues and organs. In rats, the treatment had no adverse effects with respect to mortality or gross necropsy. Body weight gain was decreased in male rats treated with 1500 (8%), 3000 (7%), or 6000 (9%) mg/kg-day and in female rats treated with 6000 mg/kg-day (10%). In mice, the treatment had no adverse effects with respect to mortality, body weight gain, or gross necropsy. High-dose mice of both sexes had decreased activity and rough coats. Because of marginal toxicity of the compound and a lack of detailed reporting of the results, no NOAEL or LOAEL were identified for rats or mice in this study.

NTP (1984) also conducted 13-week gavage studies in rats and mice. Groups of 10 male and 10 female Fischer 344/N rats (initially approximately 6 weeks of age) were treated by gavage with 0, 250, 500, 1000, 2000, or 4000 mg/kg-day of tris(2-ethylhexyl)phosphate (purity 97-99%) in corn oil 5 days/week for 13 weeks; the expanded doses were 0, 179, 357, 714, 1429, or 2857 mg/kg-day. Groups of 10 male and 10 female B6C3F1 mice (initially approximately 8 weeks of age) were treated by gavage with 0, 500, 1000, 2000, 4000, or 8000 mg/kg-day of tris(2-ethylhexyl)phosphate in corn oil 5 days/week for 13 weeks; the expanded doses were 0, 357, 714, 1429, 2857, or 5714 mg/kg-day. Parameters used to assess toxicity were mortality, clinical signs, body weight gain, and gross necropsy (all animals) and histology (control and high-dose groups, and all animals dying during the study) of major tissues and organs. In rats, the treatment had no adverse effects with respect to mortality, gross necropsy, or histology. Body weight gain was slightly decreased in high-dose male rats (5%), and female rats treated with 2000 (10%) or 4000 (5%) mg/kg-day. In mice, the deaths of 1 female treated with 1000 mg/kg-day and 3 females treated with 2000 mg/kg-day were not considered treatment-related; however, the cause of these deaths was not reported. Body weight gain was slightly decreased in high-dose male mice (7%), and female mice treated with 4000 (5%) or 8000 (5%) mg/kg-day. Inflammatory lesions of the gastric mucosa were observed in "all groups" of mice, but the severity of lesions increased in the higher dose groups; the authors did not indicate whether these lesions were observed in both control and treatment groups, or only in treatment groups. The incidences of forestomach ulceration in mice treated with 0, 500, 1000, 2000, 4000 or 8000 mg/kg-day were 0/10, 0/10, 0/10, 1/10, 0/10, and 1/10, respectively, for males, and 0/10, 0/10, 0/10, 0/10, 1/10, and 3/10, respectively, for females. This study identified the highest dose in rats, 4000 mg/kg (2857 mg/kg-day), as a NOAEL. Because of marginal toxicity of the compound and a lack of detailed reporting of the results, no NOAEL or LOAEL were identified for mice in this study.

NTP (1984) conducted 2-year gavage studies in rats and mice. Groups of 50 male and 50 female Fischer 344/N rats (initially 6-8 weeks of age) were treated by gavage with tris(2-ethylhexyl)phosphate (purity 97-99%) in corn oil 5 days/week for 2 years. Males received 0, 2000, or 4000 mg/kg; females received 0, 1000, or 2000 mg/kg. The expanded doses were 0, 1429, or 2857 mg/kg-day for male rats, and 0, 714, or 1429 mg/kg-day for female rats. Groups of 50 male and 50 female B6C3F1 mice (initially 6-8 weeks of age) were treated by gavage with 0, 500, or 1000 mg/kg of tris(2-ethylhexyl) phosphate (purity 97-99%) in corn oil 5 days/week for 2 years; the expanded doses were 0, 357, or 714 mg/kg-day. Parameters used to assess toxicity were survival, clinical signs, body weight gain, and gross necropsy and histology of major tissues and organs. In rats, the treatment had no adverse effects with respect to survival, clinical signs, or non-neoplastic lesions. Body weight gain was decreased in low- (11.5%) and high-dose (15.8%) male rats; in female rats, body weight gain was within 10% of the control group throughout the study. Equivocal evidence of carcinogenicity was observed in male rats, but none was observed in female rats. In mice, the treatment had no adverse effects with respect to survival, clinical signs, or body weight gain. The incidence of cytoplasmic vacuolization of the liver was slightly increased in low- (16/50) and high-dose (18/50) female mice, compared to the control group (10/48); however, these differences were not statistically significant (Fisher Exact Test; $p>0.05$). The incidences of follicular cell hyperplasia of the thyroid gland were significantly increased (Fisher Exact Test; $p<0.05$) in low- (12/48) and high-dose (24/47) male mice, and low- (13/47) and high-dose (12/46) female mice, compared to control group males (0/49) and females (1/44). Follicular cell hyperplasia was characterized by a focal increase in cellularity, affecting one or several follicles in the thyroid gland. Some evidence of carcinogenicity was observed in female mice, but none was observed in male mice. This study identified the lowest dose in male rats, 2000 mg/kg (1429 mg/kg-day), as a NOAEL. The lowest dose in mice, 500 mg/kg (357 mg/kg-day), was identified as a LOAEL for follicular cell hyperplasia.

Male albino rats (10/dose group; initial body weights 100-180 g) were treated in the diet with 0, 0.17, 0.7, or 2.7% tris(2-ethylhexyl) phosphate for 30 days; the authors calculated the administered doses as 0, 110, 430, or 1550 mg/kg-day (MIIR, 1944). High-dose rats had decreased food consumption (88%), probably due to decreased palatability of the treated food, and a corresponding decrease in body weight gain (81% of controls). The treatment had no adverse effects with respect to mortality, clinical signs, blood urea nitrogen, or histology of the adrenals, small intestine, kidneys, liver, spleen, or testes. This study identified a NOAEL of 0.7% (430 mg/kg-day) and a LOAEL of 2.7% (1550 mg/kg-day) for decreased food consumption and body weight gain in rats.

McFarland and Punte (1966) performed a neurotoxicology experiment in chickens. Female White leghorn chickens (4-8/dose group; initial body weights 1.5-2.3 kg) were treated once by gavage with 0, 500, or 2500 mg/kg of "Flexol" Plasticizer TOF [tris(2-ethylhexyl) phosphate, purity not reported]. The chickens were observed for 28 days after dosing, and then

sacrificed for gross necropsy of sections of the brain, three levels of the spinal cord, and the sciatic nerve. One high-dose chicken died during the study; the cause of death was not reported. The treatment had no adverse effects with respect to clinical signs, body weight gain, or neuropathology.

DERIVATION OF THE PROVISIONAL CHRONIC RfD

Chronic oral toxicity studies of tris(2-ethylhexyl) phosphate were located for rats and mice (NTP, 1984). Decreased body weight gain was observed in male rats at 1429 and 2857 mg/kg-day; no other effects were observed in male rats at those dose levels, or in female rats at 714 or 1429 mg/kg-day (NTP, 1984). Mice appeared to be more sensitive than rats to the effects of tris(2-ethylhexyl) phosphate; a dose level of 357 mg/kg-day increased the incidence of follicular cell hyperplasia in male and female mice (NTP, 1984).

Several oral toxicity studies of subchronic duration were located (NTP, 1984; MIIR, 1944); in the subchronic studies, adverse effects were observed in rats and mice at much higher dose levels (1500-6000 mg/kg-day) than in the chronic studies. Because of reporting deficiencies, short duration of treatment, and the use of small numbers of animals per treatment group, the subchronic toxicity studies were of limited use in risk assessment, and were not considered in the derivation of the provisional chronic RfD.

The chronic mouse study was selected as the key study because it established the lowest LOAEL in the data base. The critical effect in the mouse study (follicular cell hyperplasia) was observed at 357 mg/kg-day.

The provisional chronic RfD is calculated as follows:

$$\text{p-RfD} = \text{LOAEL}_{\text{ADJ}} / (\text{UF} \times \text{MF})$$

where

LOAEL = 357 mg/kg-day (representing the upper bound value in the range of mean dietary intakes, dietary plus supplemental, taken from the NHANES II data base)

UF = uncertainty factor = 3000 (10 for intraspecies, 10 for interspecies differences, 10 for the use of a LOAEL, and 3 for data base deficiencies, lack of developmental or reproductive toxicity studies)

MF = modifying factor = 1 (standard default)

thus,

p-RfD = [357 mg/kg-day]/[3000] = 0.1 = 1E-1 mg/kg-day

STATEMENT OF CONFIDENCE

Confidence in the key study is high. This is a well-conducted study using an adequate number of animals of both sexes, measuring a sufficient number of endpoints, and identifying biologically significant effects. Confidence in the data base is low. Although chronic studies were conducted in two species, a NOAEL was not identified in the most sensitive species, the identified critical effect was observed in only one species, and corroborating data for chronic toxicity of tris(2-ethylhexyl) phosphate were not available from other studies. In addition, no developmental or reproductive toxicity studies were located. Reflecting the low confidence in the data base, confidence in the provisional chronic RfD is low.

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09-10-02

Provisional Peer Reviewed Toxicity Values for

Tris(2-ethylhexyl)phosphate
(CASRN 78-42-2)

Derivation of a Chronic Inhalation RfC

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR TRIS(2-ETHYLHEXYL)PHOSPHATE (CASRN 78-42-2)
Derivation of a Chronic Inhalation RfC

Background

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INTRODUCTION

An RfC for tris(2-ethylhexyl)phosphate is not available on IRIS (U.S. EPA, 2001) or in the HEAST (U.S. EPA, 1997). No relevant documents were found in the CARA list (U.S. EPA, 1991, 1994a). ATSDR (2001) has not produced a Toxicological Profile for tris(2-ethylhexyl) phosphate. No occupational exposure limits for tris(2-ethylhexyl)phosphate have been assigned by ACGIH (2001), OSHA (2001a,b) or NIOSH (2001). The NTP status reports (NTP, 2001), IARC (2001) monograph index, an Environmental Health Criteria document on flame retardants (IPCS, 2000), and a review of esters of organic phosphorous (Bisei, 2001) were consulted for information regarding tris(2-ethylhexyl) phosphate. Computer literature searches of TOXLINE (from 1965), RTECS and TSCATS had been performed in 1994. Updated literature searches (1994 - 2001) of TOXLINE, MEDLINE, CANCERLIT, EMIC/EMICBACK,

DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September, 2001.

REVIEW OF PERTINENT LITERATURE

No studies were located regarding the systemic toxicity of tris(2-ethylhexyl) phosphate following inhalation exposure in humans. Four inhalation studies in animals were identified (MacFarland and Punte, 1966; MIIR, 1951; Mobil Oil Corp., 1991, 1994).

MacFarland and Punte, 1966

A radiotracer inhalation study observed rapid systemic absorption of tris(2-ethylhexyl)phosphate (MacFarland and Punte, 1966). A total of 9 male Wistar rats received a single 20 minute head-only exposure to aerosol [^{32}-P]-tris(2-ethylhexyl)phosphate; single animals were sacrificed after 5 or 30 minutes, 1, 4, 17, 18, 24, 48, or 70 hours. Blood, bone, muscle, fat, brain, lungs, liver, spleen, kidneys, stomach, stomach content, and head skin were analyzed for radioactivity; feces and urine were analyzed at 17 and 48 hours only. In the lung, peak retention was 13% of total activity at 5 minutes; in the brain and liver, 9% and 16%, respectively, at 30 minutes, in stomach contents, 50-64% at 1 hour. Other measured organs did not retain more than 2% of activity at any time point. Total carcass radioactivity was maximal at 48 hours, 81% retention of the total dose. Excretion was primarily fecal, and fecal radioactivity was 7% of the total dose at 17 hours.

MacFarland and Punte (1966) conducted acute inhalation experiments. Groups of 10 Wistar rats (gender not specified) were exposed to tris(2-ethylheyxl)phosphate concentrations up to 227 mg/m^3 for 210 minutes; no mortalities were observed. Groups of 10 Hartley guinea pigs received exposures ranging from 450 mg/m^3 for 30 minutes (3/10 mortalities) to 287 mg/m^3 for 120 minutes (8/10 mortalities); however, control data were not provided. The authors report an LC_{50} > 93,800 mg/min/m^3 for rats and approximately 30,000 mg/min/m^3 for guinea pigs (MacFarland and Punte, 1966).

MacFarland and Punte (1966) exposed groups of 1 male and 1 female mongrel behavior-trained dogs, 1 male and 1 female rhesus monkey, and 10 male and 10 female Hartley guinea pigs to 0, 10.8, 26.4, or 85.0 mg/m^3 of tris(2-ethylhexyl)phosphate aerosol 6 hours per day, 5 days per week for 12 weeks (60 exposures total). Mean particle size was 4.4 $\pm$ 3.0 µm. Body weight was measured weekly. Behavioral tests were conducted on dogs (conditioned avoidance response) and monkeys (visual discrimination) biweekly. Hematology and clinical chemistry were analyzed at 0, 4, 8, and 12 weeks. At sacrifice, gross necropsy, lung, liver, and kidney weight, and histology of the lung, liver, kidney, spinal cord, and sciatic nerve were performed. No adverse effects were observed in monkeys. In dogs, exposure caused changes in the

conditioned avoidance response (14/240, 0/120, 24/240, and 44/240 trials for the respective concentrations) that was statistically significantly lower at 10.8 than controls and higher than controls at 85.0 mg/m^3 of tris(2-ethylhexyl)phosphate. Mild chronic inflammatory changes were observed in the pulmonary parenchyma of exposed, but not control, dogs. The effects of exposure on guinea pigs were confounded by intercurrent respiratory infections diagnosed in all guinea pigs that died (30%, 46%, 25%, and 59%, respectively). In surviving guinea pigs, lung abnormalities were noted in control and exposed animals. Because each group was exposed in a single chamber, the relevance of the lesions observed in guinea pigs to the pulmonary inflammation seen in exposed canines was unclear. For tris(2-ethylhexyl)phosphate inhalation, this study identifies a NOAEL of 85.0 mg/m^3 in rhesus monkeys and a LOAEL of 10.8 mg/m^3 in mongrel dogs, on the basis of behavioral changes.

MacFarland and Punte (1966) conducted a subsequent inhalation study, exposing groups of 20 male Hartley guinea pigs (300-400 g start weight) to 0, 1.6, or 9.6 mg/m^3 of tris(2-ethylhexyl)phosphate aerosol 6 hours per day, 5 days per week for 12 weeks (60 exposures total); tetracycline hydrochloride was administered in the drinking water as a prophylactic. Mean particle size was 3.8 $\pm$ 1.7 μm. Appearance and behavior were observed daily; body weights were measured weekly. At sacrifice, hematology and serum clinical chemistry, lung, liver, and kidney weight, and histopathology of the lung, liver, spinal cord, and sciatic nerve were measured. One control and one animal exposed to 1.6 mg/m^3 died. At sacrifice, statistically significant decreases in kidney-to-body weight at 1.6 or 9.6 mg/m^3 and increased mean body weight at 9.6 mg/m^3 compared to controls were observed. Histopathological examination revealed inconsistent renal parenchymal changes in animals exposed to 9.6 mg/m^3 of tris(2-ethylhexyl)phosphate. Based on EPA (1994b), relative organ weight does not appear to be a clearly toxic effect, so 9.6 mg/m^3 is considered a LOAEL in male guinea pigs.

Other Studies

Three inhalation studies provide insufficient information for evaluation. MIIR (1951) reported exposing groups of 6 rats (strain, and gender not provided) for 30 minutes, 1 or 2 hours to cooling vapor saturated by tris(2-ethylheyxl)phosphate heated to 170ºC. At 30 minutes, no rats died; at 1 hour, 2/6 died; and at 2 hours, all animals died. Exposure to saturated vapors at room temperature did not cause mortalities. Control data and concentration data were not provided. Mobil Oil Corp. (1994) exposed rats to an aerosol mixture of tris(2-ethylheyxl)phosphate, triethanolamine, and diethanolamine for 2 weeks. Treatment caused increased lung weight, increased numbers of pulmonary alveolar macrophages, and enlargement of lung-associated lymph nodes. Because animals were exposed to multiple compounds, these results cannot be evaluated. Groups of 10 male rats were exposed 6 hours per day, 5 days per week for 2 weeks to an oil containing tris(2-ethylheyxl)phosphate; no evidence of micronucleation was detected in femur marrow red blood cells (Mobil Oil Corp., 1991). Other

endpoints were not reported. Because the constitution of the test substance is unclear, these results cannot be evaluated.

FEASIBILITY OF DERIVING A PROVISIONAL RfC

The 12 week inhalation studies in Hartley guinea pigs, dogs, and monkeys (MacFarland and Punte, 1966) are inadequate to derive a p-RfC. Inadequate numbers of dogs and monkeys were used. Histopathological examination of only 4 tissues was conducted; although the lungs were examined, the upper respiratory tract was not. Although statistical significance was provided for the critical effects, numerical means were not reported for comparison. No other potentially suitable studies were located.

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09-10-2002

Provisional Peer Reviewed Toxicity Values for

Tris(2-ethylhexyl)phosphate
(CASRN 78-42-2)

Derivation of a Carcinogenicity Assessment

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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

09-10-2002

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR TRIS(2-ETHYLHEXYL)PHOSPHATE (CASRN 78-42-2)
Derivation of a Carcinogenicity Assessment

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

No cancer assessment for tris(2-ethylhexyl)phosphate is available on IRIS (U.S. EPA, 2001) or in the HEAST (U.S. EPA, 1997) or Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). No documents for tris(2-ethylhexyl)phosphate are included on the CARA list (U.S. EPA, 1991, 1994). IARC has not produced a carcinogenicity assessment for tris(2-ethylhexyl)phosphate. ATSDR (2001) has no Toxicological Profile for this compound. The NTP (2001) status report, an Environmental Health Criteria document on flame retardants (IPCS, 2000), and a review of esters of organic phosphorous (Bisei, 2001) were consulted for information. Computer literature searches of TOXLINE (from 1981), HSDB, RTECS and TSCATS had been performed in 1992 and updated in April, 1994. Computer literature searches of TOXLINE (from 1981), HSDB, RTECS and TSCATS had been performed in 1992 and updated in April, 1994. Update literature searches (1994 - 2001) of TOXLINE, MEDLINE,

CANCERLIT, EMIC/EMICBACK, DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September, 2001.

REVIEW OF PERTINENT DATA

Human Studies

No studies were located regarding the carcinogenicity of tris(2-ethylhexyl)phosphate following inhalation or oral exposure in humans.

Animal Studies

NTP (1984) conducted 2-year gavage studies in rats and mice. Groups of 50 male and 50 female Fischer 344/N rats (intially 6-8 weeks of age) were treated by gavage with tris(2-ethylhexyl)phosphate (purity 97-99%) in corn oil 5 days/week for 2 years. Males received 0, 2000, or 4000 mg/kg; females received 0, 1000, or 2000 mg/kg. The expanded doses were 0, 1429, or 2857 mg/kg-day for male rats, and 0, 714, or 1429 mg/kg-day for female rats. Groups of 50 male and 50 female B6C3F1 mice (initially 6-8 weeks of age) were treated by gavage with 0, 500, or 1000 mg/kg of tris(2-ethylhexyl)phosphate (purity 97-99%) in corn oil 5 days/week for 2 years; the expanded doses were 0, 357, or 714 mg/kg-day. Parameters used to assess toxicity were survival, clinical signs, body weight gain, and gross necropsy and histology of major tissues and organs.

In rats, treatment had no adverse effects with respect to survival, clinical signs, or non-neoplastic lesions. Body weight gain was decreased in low- (11.5%) and high-dose (15.8%) male rats; in female rats body weight gain was within 10% of the control group throughout the study. Thus, the MTD was probably achieved in male rats, but was apparently not achieved in female rats. Benign adrenal pheochromocytomas in male rats had a significant, positive, dose-related trend, and the incidences were significantly increased in the low- (9/50) and high-dose (12/50) groups, compared to the control group (2/50). Two additional high-dose male rats had malignant adrenal pheochromocytomas; thus, the incidence of combined benign and malignant adrenal pheochromocytomas was 14/50 in high-dose male rats. The authors indicated that the incidence of adrenal pheochromocytomas observed in the concurrent control group equaled the lowest ever reported. The incidence of adrenal pheochromocytomas in treated male rats (18-28%) was similar to that of historical controls (202/1135; 18%). Although the incidence of malignant adrenal pheochromocytomas in high-dose male rats (4%) was higher than the historical incidence (10/1135; 0.9%), it is difficult to determine the biological significance of this tumor in only 2 rats. The authors concluded that the increase in adrenal pheochromocytomas in male rats was not clearly related to administration of the test compound. Adrenal pheochromocytomas in low- (2/50) and high-dose (1/50) female rats occurred at similar frequencies as that of the control

group (2/50). A significant, positive, dose-related trend was observed in follicular cell adenoma, cystadenoma, or carcinoma in male rats, but the incidences in the low- (2/49) and high-dose (6/49) groups were not significantly different from that of the control group (1/46). The authors did not consider the increased incidence of follicular cell tumors to be treatment-related. One high-dose male rat (1/50 incidence) had a malignant, mixed salivary gland tumor; although the historical incidence of this tumor in control rats is extremely low (1/2000), the biological significance of this tumor in only one rat is not known. Incidences of acinar cell adenoma in low- (5/48) and high-dose (2/49) male rats and mammary gland tumors in low-dose (2/50) female rats were significantly lower than those of the control group (14/50 for acinar cell adenoma; 11/50 for mammary tumors). The incidence of acinar cell adenoma was unusually high in the control group (28%), and incidences in the treated groups (4-10%) were similar to that of historical controls (37/1128; 3%). Thus, the authors did not consider the decreased incidence of acinar cell adenoma to be treatment-related. The authors concluded that there was "equivocal evidence of carcinogenicity" in male rats and "no evidence of carcinogenicity" in female rats exposed to tris(2-ethylhexyl)phosphate.

In mice, the treatment had no adverse effects with respect to survival, clinical signs, or body weight gain. The incidence of cytoplasmic vacuolization of the liver was slightly increased in low- (16/50) and high-dose (18/50) female mice, compared to the control group (10/48); however, these differences were not statistically significant (Fisher Exact Test conducted for NCEA; $p>0.05$). The incidences of follicular cell hyperplasia of the thyroid gland were significantly increased (Fisher Exact Test conducted for NCEA; $p<0.05$) in low- (12/48) and high-dose (24/47) male mice, and low- (13/47) and high-dose (12/46) female mice, compared to control group males (0/49) and females (1/44), indicating that the MTD was probably achieved in mice at both dose levels. Follicular cell hyperplasia was characterized by a focal increase in cellularity, affecting one or several follicles in the thyroid gland. Female mice had a significant, positive, dose-related trend in occurrence of hepatocellular carcinomas, and the incidence of these tumors was significantly higher in high-dose female mice (7/50) than in the control group (0/50); the incidence of hepatocellular carcinomas in low-dose female mice (4/50) was not significantly different from that of the control group. The historical incidence of hepatocellular carcinomas in female mice was reported to be 34/1176 (3%). Female mice had a significant, positive, dose-related trend in the occurrence of combined hepatocellular adenoma/carcinoma, and the incidence of these tumors was significantly higher in high-dose female mice (10/50), but not in low-dose female mice (8/50), compared to the control group (2/48). The historical incidence of combined hepatocellular adenoma/carcinoma in female mice was reported to be 80/1176 (7%). Incidences of hepatocellular carcinomas in low- (12/50) and high-dose (12/49) male mice were similar to that of the control group (9/50). Incidences of hemangiosarcoma in low- (0/50) and high-dose (1/49) male mice, and malignant lymphomas (6/50) and pituitary adenomas (2/47) in high-dose female mice were significantly lower than those of the control group (7/50 for hemangiosarcoma; 14/49 for malignant lymphomas; 6/41 for pituitary adenomas). The authors indicated that the decreased incidence of hemangiosarcoma in male

mice was of questionable significance because of similar incidences between treated groups (0-2%) and historical controls (44/1090; 4%). The authors concluded that there was "some evidence of carcinogenicity" in female mice and "no evidence of carcinogenicity" in male mice exposed to tris(2-ethylhexyl)phosphate.

Genotoxicity Studies

Tris(2-ethylhexyl)phosphate did not produce genotoxic effects in the following studies: mutagenicity assays with the TA98, TA100, TA1535, and TA1537 strains of *Salmonella typhimurium* (Zeiger et al., 1985; Bayer, 1982); a mouse lymphoma test with L5178Y cells (Myhr and Caspary, 1991); a replicative DNA synthesis assay in mouse hepatocytes (Miyagawa et al., 1995); sister chromatid exchange and chromosomal aberration assays in Chinese hamster ovary (CHO) cells (Ivett et al., 1989); a BALB/c-3T3 cell transformation assay (Matthews et al., 1993), or a Syrian hamster embryo cell transformation assay (LeBoeuf et al., 1996). Tris(2-ethylhexyl)phosphate did not cause micronucleus formation in an *in vivo* bone marrow micronucleus assays in rats and mice (Mobil Oil, 1991; Shelby et al., 1993) and was not genotoxic in a *Drosophilia* dominant lethal mutation assay (Foureman et al., 1994).

SAR Relationships

Kluwe et al. (1985) reviewed the chronic toxicity and carcinogenicity of several 2-ethylhexyl compounds: tris(2-ethylhexyl)phosphate, di(2-ethylhexyl)phosphate, di(2-ethylhexyl)adipate, and sodium 2-ethylhexylsulfate. All of the compounds examined had some hepatocarcinogenic activity: tris(2-ethylhexyl)phosphate increased the incidence of hepatocellular tumors in female mice; di(2-ethylhexyl) phthalate increased the incidence of hepatocellular tumors in male and female rats and mice; di(2-ethylhexyl)adipate increased the incidence of hepatocellular tumors in male and female mice; and 2-ethylhexyl sulfate was equivocal for increased incidence of hepatocellular tumors in female mice. Moreover, decreases in the incidence of mammary fibroadenomas were observed in female rats receiving tris(2-ethylhexyl)phosphate, di(2-ethylhexyl)phosphate, and di(2-ethylhexyl)adipate (but not sodium 2-ethylhexylsulfate). Because of the apparent structure-activity relationship, the authors hypothesized that 2-ethylhexyl compounds may share a common carcinogenic mode of action. Kluwe et al. (1985) speculate that the metabolic production of 2-ethylhexanol may increase hepatic peroxisome proliferation and thereby induce hepatic tumor formation. However, the metabolism of tris(2-ethylhexyl)phosphate has not been studied and the extent of *in vivo* conversion of tris(2-ethylhexyl)phosphate to 2-ethylhexanol is unknown. Subsequently, Astill et al. (1996) found that 2-ethylhexanol induced hepatocellular carcinomas in female mice. Thus, the available SAR data provides inconclusive, but supportive, evidence for hepatocarcinogenicity of tris(2-ethylhexyl)phosphate in mice.

WEIGHT-OF-EVIDENCE DESCRIPTOR

There are no data regarding the carcinogenicity of tris(2-ethylhexyl)phosphate in humans. Limited evidence of carcinogenicity exists in animal studies, as indicated by a moderate increase in the incidence of hepatocellular tumors in female B6C3F1 mice (NTP, 1984), and an equivocal increase in the incidence of adrenal pheochromocytomas in male Fischer 344 rats (NTP, 1984). In addition, a proposed SAR-related mechanism for induction of hepatocellular tumors by tris(2-ethylhexyl)phosphate provides supporting evidence for carcinogenicity (Kluwe et al., 1985). Tris(2-ethylhexyl)phosphate does not appear to be genotoxic *in vitro* or *in vivo*.

Under the proposed guidelines (U.S. EPA, 1999), these data constitute suggestive evidence of carcinogenicity.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Oral Slope Factor

The NTP (1984) performed carcinogenicity studies on orally administered tris(2-ethylhexyl)phosphate in Fischer 344 rats and B6C3F1 mice. The incidence of combined adrenal pheochromocytomas (benign and malignant) in male rats treated with 1429 or 2857 mg/kg-day was increased with respect to the concurrent controls, with a significant positive trend. However, the incidence of this tumor in concurrent controls was unusually low, and the incidence in treated rats was similar to that of historical controls. Thus, the authors concluded that this incidence was not clearly related to treatment and tris(2-ethylhexyl)phosphate was "equivocal for carcinogenicity" in male rats. The incidence of combined hepatocellular adenomas/carcinomas was increased in female mice at 714 mg/kg-day, but not at 357 mg/kg-day, with respect to the concurrent controls, and a significant positive trend was observed. The authors concluded that there was "some evidence of carcinogenicity" in female mice. The authors indicated that the study did not provide "clear evidence of carcinogenicity" because the increase in hepatocellular tumors in female mice was observed only at the high-dose level, and was moderate in magnitude.

Using the linearized multistage model, a provisional slope factor for hepatocellular tumors in female mice of 3.2E-3 $(mg/kg\text{-}day)^{-1}$ was derived, as shown below. The Drinking Water Unit Risk is 9.1E-8 $(ug/L)^{-1}$. Concentrations associated with risk levels of 1E-4, 1E-5, and 1E-6 are 1.1E+3, 1.1E+2, and 1.1E+1, respectively. As described in the proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996, 1999) a slope factor of 3.0E-3 $(mg/kg\text{-}day)^{-1}$ was calculated by dividing 0.1 by the LED_{10} of 33.4 mg/kg-day. As the slope factors calculated by the different methods are not appreciably different, no additional unit risk calculations were performed.

The key study was well-conducted with the compound administered to rats and mice of both sexes at 2 dose levels. The MTD was probably achieved at both dose levels in mice and male rats, but was apparently not achieved in female rats. The initial number of animals per group and the number of animals surviving until study termination were adequate to examine risk from late-forming tumors. Animals were exposed for 2 years (their life expectancy), a relevant route of exposure was used, and a sufficient number of endpoints were examined. However, the tumor type used for derivation of the provisional slope factor was observed in only one species and one study; corroborating data for the carcinogenicity of tris(2-ethylhexyl)phosphate were not available from other animal studies. The carcinogenic response observed in mice was only moderate in magnitude, and was equivocal in rats. In addition, no data on carcinogenicity of tris (2-ethylhexyl) phosphate were available from human studies.

I. Tumor type -- combined hepatocellular adenoma/carcinoma
Test Animals -- mice, B6C3F1, female
Route -- oral, gavage
Reference -- NTP, 1984

Experimental doses (mg/kg)	Body Weight (Kg)	Length of Exposure	Transformed Animal Dose[a] (mg/kg-day)	Equivalent Human Dose[b] (mg/kg-day)	Incidence (No. responding/ No. examined)
0	0.0335	104 weeks	0	0	2/48
500	0.0323	104 weeks	357	52.3	8/50
1000	0.0328	104 weeks	714	105	10/50

[a]adjusted for dosing schedule (5 days/week)
[b]equivalent human dose = transformed animal dose x (animal body weight/70 kg)$^{1/4}$

Provisional Oral Slope Factor (q1*)-- **3.2E-3 (mg/kg-day)$^{-1}$**

LED_{10} -- 33.4 mg/kg-day

$0.1/LED_{10}$ = 3.0E-3 (mg/kg-day)$^{-1}$

Drinking Water Unit Risk -- 9.1E-8 per ug/L[a]

Extrapolation Method -- Linearized Multistage Procedure

[a]drinking water unit risk (at 1 ug/L)= [(q1*/70 kg) x 2L/day]/1000 ug/mg.

Drinking Water Concentrations at Specified Risk Levels[a]:

Risk Level	Concentration (ug/L)
E-4 (1 in 10,000)	1.1E+3
E-5 (1 in 100,000)	1.1E+2
E-6 (1 in 1,000,000)	1.1E+1

[a]drinking water concentrations associated with a specific risk level are calculated by [[(risk level/q1*) x 70 kg]/2 L/day] x 1000 ug/mg.

Inhalation Unit Risk

Inhalation data upon which to base an inhalation unit risk are not available. It is not recommended to derive a provisional inhalation unit risk for tris(2-ethylhexyl)phosphate based on the provisional oral slope factor. Route-to-route extrapolation is precluded by the lack of information regarding pharmacokinetics (e.g., potential absorption differences via the two routes, potential first pass effects by the oral route, metabolism) and the possibility of portal-of-entry effects.

The likelihood of irritant effects at the portal of entry (respiratory tract) following inhalation exposure is supported by inflammation and mucosal ulceration in mice in the subchronic, but not the chronic, gavage study conducted by NTP (1984) and by positive irritant responses reported in rabbits and guinea pigs following acute dermal exposure (MIIR, 1944; Eastman Kodak Co., 1979). Structurally-related chemicals such as di(2-ethylhexyl)phthalate (DEHP), di(2-ethylhexyl)adipate (DEHA) and 2-ethylhexanol are also slight-to-moderate skin irritants (Rowe and McCollister, 1981; Sandmeyer and Kirwin, 1981). Since the dose producing the irritant effect, as well as the tissue reaction to the irritant (e.g., cytotoxicity), is dependent on the route of administration, route extrapolation of irritants may not be appropriate. Information as to whether structurally-related chemicals (DEHP, DEHA) induce a tumorigenic response in the respiratory system when inhaled is not readily available (U.S. EPA, 1995, 1997). Whether the respiratory tract may therefore be susceptible to tumor induction by the inhalation route cannot be addressed for this chemical.

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