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Provisional Peer-Reviewed Toxicity Values for

Tris(1-chloro-2-propyl)phosphate
(CASRN 13674-84-5)

Superfund Health Risk Technical Support Center
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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
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
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TRIS(1-CHLORO-2-PROPYL)PHOSPHATE (CASRN 13674-84-5)

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 Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

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.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

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. Environmental Protection Agency (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.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Tris(1-chloro-2-propyl)phosphate (TCPP) belongs to a class of chemicals known as trisphosphates, more specifically, aliphatic halogenated trisphosphates (NICNAS, 2001). Trisphosphates are primarily used industrially as flame retardants, plasticizers, and solvents (NICNAS, 2001). TCPP is used as a flame retardant in polyurethane foam (OECD, 2000). Figure 1 provides the chemical structure for TCPP. A table of physicochemical properties is provided below (see Table 1).

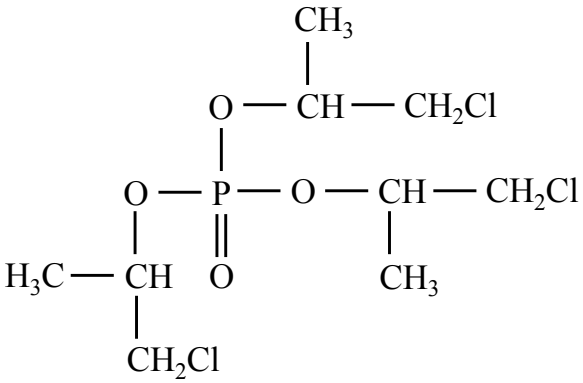


Figure 1. Tris(1-chloro-2-propyl)phosphate Structure

Table 1. Physicochemical Properties for TCPP (CASRN 13674-84-5)[a]

Property (unit)	Value
Boiling point (ºC)	Not available
Melting point (ºC)	−40
Density (g/cm^3)	1.29
Vapor pressure (Pa at 25ºC)	<260
pH (unitless)	Not available
Solubility in water (g/L at 20ºC)	1.6
Relative vapor density (air = 1)	Not available
Molecular weight (g/mol)	327.6

[a]NICNAS (2001).

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for TCPP is included on the EPA's Integrated Risk Information System (IRIS) database (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values were reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011b). The Chemical Assessments and Related Activities (CARA) list did not include a Health and Environmental Effects Profile (HEEP) for TCPP (U.S. EPA, 1994a). The

Agency for Toxic Substances and Disease Registry (ATSDR) is in the process of reviewing the toxicity of TCPP in conjunction with other phosphate ester flame retardants, and a draft Toxicological Profile is available (ATSDR, 2009). No minimal risk levels were reported for TCPP due to lack of adequate information. The World Health Organization (WHO) reviewed the toxicity of TCPP in an Environmental Health Criteria document (IPCS, 1998) and indicated that adverse health effects are negligible due to low exposure risk. The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to TCPP. No occupational exposure limits for TCPP have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), proposed by the National Institute of Occupational Safety and Health (NIOSH, 2011), or adopted by the Occupational Safety and Health Administration (OSHA, 2006).

The HEAST (U.S. EPA, 2011b) does not report a cancer weight-of-evidence (WOE) classification or an oral slope factor for TCPP. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of TCPP. TCPP is not included in the *12th Report on Carcinogens* (NTP, 2011c). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for TCPP.

Literature searches were conducted on sources published from 1900 through September 13, 2011 for studies relevant to the derivation of provisional toxicity values for tris(1-chloro-2-propyl)phosphate (TCPP), CAS No. 13674-84-5. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Contents database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for TCPP and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. The phrase "statistical significance," used throughout the document, indicates a p-value of <0.05.

Table 2. Summary of Potentially Relevant Data for TCPP (CASRN 13674-84-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							
Animal								
1. Oral (mg/kg-d)								
Subchronic	20/20, CD rat, diet, 90 d	Males: 0, 36, 112, 337, 944; Females: 0, 43, 120, 399, 1222[c] (Adjusted)	Increased liver weight in males[d]	ND	NDr	36[e]	Freudenthal and Henrich (1999) Compound used was 70% TCPP; doses are adjusted for TCPP content.	

Table 2. Summary of Potentially Relevant Data for TCPP (CASRN 13674-84-5)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
	10/10 B6C3F$_1$ mice, diet, 14 wk	**Males: 0, 219, 456, 737, 2470, 4410** **Females: 0, 198, 420, 906, 1930, 3590 (Adjusted)**	**Decreased terminal body weight; increased relative liver weight in males** **Hepatocyte hypertrophy in males**	**219** **737**	**NDr** **138**	**456** **2470**	**NTP (2011a,b)**	**PS**
Chronic	ND							
Developmental	0/11−14, Wistar rat, diet, GD 0−20	0, 6.7, 69, 670 tris(chloropropyl)phosphate (Adjusted)	Missing 13th rib in fetuses	69[e]	278	670	Kawasaki et al. (1982)[f] Compound used was tris(chloro-propyl)phos-phate, a mixture that contains TCPP. Doses are not corrected for TCPP content because sufficient information was not available.	
Reproductive	ND							
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

Table 2. Summary of Potentially Relevant Data for TCPP (CASRN 13674-84-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]Notes: PS = Principal study.
[c]Compound tested was administered in the diet and stated to contain 70% TCPP; therefore, doses are adjusted by the formula:
$Dose_{ADJ}$ = [Dose in ppm × Average Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days)] × 0.7.
[d]The critical effect was not specified in the report, but the information provided indicates that it was liver weight.
[e]These values were not reported by the study authors but are determined by the data.
[f]This was published in a foreign journal, but a translation was provided by the National Institute of Health Science (NIHS, 1994).
ND = No data, NDr = Not determined.

HUMAN STUDIES

Oral Exposures

No human oral exposure studies on TCPP were identified.

Inhalation Exposures

No human inhalation exposure studies on TCPP were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to TCPP have been evaluated in two subchronic studies (Freudenthal and Henrich, 1999; NTP, 2011a,b) and one developmental study (Kawasaki et al., 1982). Three short-term studies (Kawasaki et al., 1982; Bayer, 1993; Stauffer Chemical Company, 1980a) were also identified and are summarized in the section titled "OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)."

Subchronic Studies

Freudenthal and Henrich, 1999

Freudenthal and Henrich (1999) conducted a subchronic study in rats. CD rats (20/sex/treatment group) were administered 0-, 800-, 2500-, 7500-, or 20,000-ppm Fyrol PCF—which was stated in the description of the 7-day Stauffer Chemical Company (1980a) study to contain 70 ± 5% TCPP and 22 ± 5% 2-chloropropanol phosphate—via the diet for 13 weeks. Average daily Fyrol PCF consumption was calculated by the study authors based on weekly food consumption measurements; daily Fyrol PCF consumption in male rats was 0, 52, 160, 481, and 1349 mg/kg-day and in female rats it was 0, 62, 171, 570, and 1745 mg/kg-day. Because the compound was stated to contain only 70% TCPP, average daily TCPP intakes were equivalent to 0, 36, 112, 337, and 944 mg/kg-day in males and 0, 43, 120, 399, and 1222 mg/kg-day in females. Animals were examined for clinical signs of toxicity twice daily. Food consumption and body weight were measured weekly. Hematology and clinical chemistry parameters were measured in 10 males and 10 females per dose group at study initiation, mid-study, and termination; parameters measured included hemoglobin, packed cell volume, total erythrocyte count, total leukocyte count, total platelet count, mean corpuscular volume, differential leukocytes, blood urea nitrogen, lactate dehydrogenase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, inorganic phosphates, alkaline phosphatase, creatinine, bilirubin, cholesterol, glucose, albumin, total protein, sodium concentration, potassium concentration, and chloride concentration. Urinalysis was performed mid-study and at termination and examined color, turbidity, specific gravity, pH, glucose, and ketones; the study authors mention that other endpoints were also measured but do not specify what they were. Cholinesterase activity was determined in plasma and erythrocytes at study initiation, mid-study, and at termination, and in brain at termination. Organ weights were obtained during necropsy for the brain, adrenals, heart, liver, kidneys, gonads, and thymus. Histopathologic examination was performed on the adrenal glands, brain, epididymides, esophagus, eyes, heart, intestine, kidneys, liver, lungs, lymph nodes, mammary gland, sciatic nerve, ovaries, pancreas, pituitary gland, prostate, salivary glands, spinal cord, stomach, spleen, testes, thymus, thyroid, tibiofemoral joint, trachea, urinary bladder, uterus, and vagina.

There were no effects on mortality, clinical signs of toxicity, food consumption, hematology, clinical chemistry, urinary parameters, or cholinesterase activity. Body weight was statistically significantly lower than controls in the high-dose group (944 mg/kg-day in males, 1222 mg/kg-day in females) during Weeks 4−12 for males and 6−12 for females (see Table B.1); only in females was this change greater than 10%. Absolute and relative liver weights were increased 15−42% in all treated male rats (i.e., ≥36 mg/kg-day) and 17−33% in female rats at ≥399 mg/kg-day (see Table B.2). In the high-dose group, swelling of the periportal hepatocytes was observed in 9 male and 8 female rats; this change was only statistically significant for the males due to elevated incidence in the control females (see Table B.3). The study authors considered this change to be mild and of no toxicological significance. Relative kidney weights were increased 13−16% in males at ≥337 mg/kg-day. Kidney weights were unaffected in females. Histopathology of the kidney revealed mild cortical tubular degeneration in males at ≥337 mg/kg-day and females at 1222 mg/kg-day; statistical significance of these changes was not discussed (see Table B.3). Other histopathological changes noted included mild thyroid follicular hyperplasia (males in all groups and Fyrol PCF-treated female rats); the study authors considered this change nontreatment related due to its occurrence in male control rats (see Table B.3). The study authors indicate a NOEL of 2500 ppm (112 mg/kg-day in males and 120 mg/kg-day in females); however, it is unclear what data this NOEL was based on. A LOAEL of 36 mg/kg-day based on increased relative and absolute liver weights in male rats is identified for this review. A NOAEL was not identified.

NTP, 2011a,b

The study by NTP (2011a,b) is selected as the principal study for the derivation of the screening subchronic p-RfD and the screening chronic p-RfD. The National Toxicology Program conducted a 14-week study in mice (NTP, 2011a,b). At the time that this document was prepared, the final report was not available from NTP. However, the study abstract and summary tables were provided upon request for use in this review (NTP, 2011a). In addition, detailed mortality and body weight tables from this study were available on the NTP Web site (NTP, 2011b). TCPP (95.7% purity) was administered at concentrations of 0, 1250, 2500, 5000, 10,000, and 20,000 ppm in dosed feed to $B6C3F_1$ mice (10/sex/group) for 14 weeks. Average daily TCPP consumption was calculated based on average food consumption and body weight values reported in the study; doses were 0, 219, 456, 737, 2470, and 4410 mg/kg-day for males, and 0, 198, 420, 906, 1930, and 3590 mg/kg-day in females. Clinical observations, body weights, and food consumption were recorded weekly and prior to study termination. For females in the 0-, 906-, 1930- and 3590-mg/kg-day groups, vaginal smears were prepared on the last 16 days of the study; for males in the 0-, 737-, 2470-, and 4410-mg/kg-day groups, sperm motility and count were determined at necropsy. At termination, mice were necropsied and examined for gross abnormalities, blood was drawn for hematology and micronuclei assay, selected organs were weighed, and histopathological examinations were performed.

No treatment-related mortality or abnormal clinical signs occurred during the 14 weeks of the study (NTP, 2011a). Body weights were decreased in males and females in a time- and dose-dependent manner (NTP, 2011b). In males, body weight was decreased relative to control values by >10% from Weeks 2−14 at the highest dose (4410 mg/kg-day), from Weeks 6−14 at 2470 mg/kg-day, from Weeks 8−14 at 737 mg/kg-day, and on Week 10 and Weeks 12−14 at 456 mg/kg-day. At study termination, the average weight of the highest dose group was approximately 29% lower than controls. In females, body weight was decreased relative to

control values by >10% from Weeks 3−14 at the highest dose (3590 mg/kg-day); additional decreases in body weight in excess of 10% occurred at Week 2 for the 420-mg/kg-day group and the 906-mg/kg-day group and at Week 14 for the 198-mg/kg-day group. Average body weights for males and females over the course of the study are presented in Tables B.4 and B.5, respectively. These changes in body weight were not related to food consumption; food consumption in TCPP treated groups was increased 3−15% over controls for females and 4−28% over controls for males (see Table B.6) (NTP, 2011a).

Relative liver weight was statistically significantly increased at all doses in males and at 198, 906, 1830, and 3590 mg/kg-day in females (NTP, 2011a). Values were reported only as average percent change from controls. Changes of greater than 10% occurred at ≥456 mg/kg-day in males and ≥906 mg/kg-day in females (see Table B.6). No other changes in organ weight were reported. Hepatocyte hypertrophy was observed in male mice at doses ≥456 mg/kg-day and in female mice at doses ≥906 mg/kg-day, with changes reaching statistical significance at ≥2470 mg/kg-day in males and ≥906 mg/kg-day in females. Incidence of hepatocyte hypertrophy was dose related (see Table B.6). No other histopathological changes were noted. The only noted changes in hematological parameters were decreases in leukocyte counts of multiple lineages. These values were reported only as percent change from control where statistically significant changes occurred. In females treated with 3590-mg/kg-day TCPP, white blood cells (WBC) were decreased 19% relative to controls, lymphocytes (LYM) were decreased 19%, neutrophils (SEG) were decreased 19%, and eosinophils (EOS) were decreased 13%. In males, WBC were decreased 10% at 2470 mg/kg-day and 48% at 4410 mg/kg-day, LYM were decreased 6% at 2470 mg/kg-day and 51% at 4410 mg/kg-day, SEG were decreased 24% at 2470 mg/kg-day and 30% at 4410 mg/kg-day, EOS were decreased 25% at 2470 mg/kg-day and 67% at 4410 mg/kg-day, and monocytes were decreased 70% at 4410 mg/kg-day.

Based on increased relative liver weight and decreased body weight in male mice, a LOAEL of 456 mg/kg-day and a NOAEL of 219 mg/kg-day are identified.

Chronic Studies

There is no suitable information to provide in this regard.

Developmental Studies

Kawasaki et al., 1982

Kawasaki et al. (1982) conducted a developmental study in rats that was published in a foreign journal in Japanese. NIHS (1994) provides a translation of the Japanese paper by Kawasaki et al. (1982); however, the poor quality of the copy made data tables difficult to read. The original source (Kawasaki et al., 1982) was unavailable for review at the time this review was prepared. It is unknown if it was peer reviewed. Pregnant female Wistar rats were administered diets containing 0, 0.01, 0.1, or 1.0% tris(chloropropyl)phosphate, which is described by the study authors as a mixture of the following four products: tris(1-chloromethylethyl)phosphate (a synonym for TCPP), bis(1-chloromethyl)(2-chloropropyl)phosphate, bis(2-chloropropyl)(1-chloromethyl)phosphate, and tris(2-chloropropyl)phosphate (relative abundance of each chemical species was not indicated)—from Gestational Day (GD) 0 to GD 20. This is estimated to be equivalent to approximately 0, 6.7, 69, or 670 mg/kg-day. This is based on the average food consumption

provided by the study authors, which was used to calculate the grams of tris(chloropropyl)phosphate consumed; however, the study authors did not provide body weight. Because body weight gains were >100 g and animals were pregnant, use of the average body weight provided by U.S. EPA (1994b) would be too low (i.e., 0.156 kg). To calculate the estimated daily intake of tris(chloropropyl)phosphate, the initial body weight was assumed to be equal to the control body weight in the 7-day experiment from the same study (0.212 kg). An average weight over the course of the study was then calculated based on the reported weight gains for each dose group and an assumption of a consistent rate of weight gain throughout the 20 days of the study. Dams (11−14/treatment) were sacrificed on GD 20. Dams were examined for implantation, fetal sex ratio, and fetal mortality. Dam body weight was also measured. The body weight of live fetuses was measured. Two thirds of the live fetuses from a litter were prepared for skeletal examinations, and the remaining third were examined for visceral abnormalities. Some dams (5−7) were allowed to deliver and litters were culled to eight pups. The pups were weaned at 21 days and monitored for an additional 7 days (until 4 weeks of age).

Data tables were difficult to read due to the poor quality of the copy. There were no treatment-related effects on body weight (only body weight gain was provided) or food consumption. No effects on dams were noted. There was no increase in fetal mortality. There were no statistically significant differences in the number of implantations, resorptions, or fetal weight. Although there were no statistically significant increases in skeletal abnormalities, treated animals had a low incidence (1−6%) of cervical ribs and missing 13th ribs that was apparently dose dependent. There were no changes in visceral abnormalities. There were no abnormalities noted in the animals observed for 4 weeks after delivery and there were no changes in the pup growth rate. The study authors did not consider tris(chloropropyl)phosphate to be teratogenic; however the dose-related 6% increase in the incidence of missing 13th ribs at 670 mg/kg-day is considered biologically significant. The NOAEL is considered to be 69 mg/kg-day with a LOAEL of 670 mg/kg-day.

Reproductive Studies

No reproductive toxicity studies on TCPP were identified.

Carcinogenicity Studies

No carcinogenicity studies on TCPP were identified.

Inhalation Exposures

No inhalation exposure studies on TCPP were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The majority of the genotoxicity and mutagenicity studies were negative (see Table 3A). All studies in bacteria and yeast were negative (Stauffer Chemical Company, 1978a; Nakamura et al., 1979; Mehlman et al., 1980; Zeiger et al., 1992; Follman and Wober, 2006). One mouse lymphoma assay was negative (Stauffer Chemical Company, 1978b), while the other was positive only in the presence of S9 (Mobil Oil Corporation, 1981). However, a memo from Albright and Wilson Americas (1989) stated that this study was incomplete. Additionally, both of these studies were conducted with industrial grade chemicals (two different sources) that are only approximately 75 ± 10% TCPP (OECD, 2000); it is unknown how other chemical species

or impurities in these mixtures impact toxicity. Three BALB/3T3 cell transformation assays were conducted. One of the studies had a nondose-related increase in cell transformation at concentrations of 0.039−0.312 µL/mL with cytotoxicity observed at 0.625 µL/mL (Stauffer Chemical Company, 1978c), while two of the studies were negative with maximum concentrations of 0.02−3.00 µL/mL used (Stauffer Chemical Company, 1978d, 1980b). A comet assay was also negative (Follman and Wober, 2006), but an unscheduled DNA test had ambiguous and equivocal results (Stauffer Chemical Company, 1978e). Chromosomal aberrations were also not induced in male Sprague-Dawley rats (Stauffer Chemical Company, 1978f).

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

The neutral red uptake test in V79 hamster fibroblast cells demonstrated that TCPP was only cytotoxic at relatively high concentrations in the presence of S9 (Follman and Wober, 2006) (see Table 3B). In the absence of S9, cytotoxicity was not observed with the highest concentration tested (10 mM). TCPP was not found to have estrogenic or antiestrogenic properties in vitro (Follman and Wober, 2006) (see Table 3B).

Short-term Studies

Kawasaki et al., 1982

Kawasaki et al. (1982) conducted a short-term study in rats that is published in a foreign language journal in Japanese. The National Institute of Health Science (NIHS, 1994) provides a translation of the Japanese paper by Kawasaki et al. (1982), however the poor quality of the copy made data tables difficult to read. The original source (Kawasaki et al., 1982) was unavailable at the time this review was prepared. It is unknown if it is peer reviewed, and the study does not state whether it was Good Laboratory Practice (GLP) compliant. Female Wistar rats (5/treatment group) were administered 0, 8, 40, 200, or 1000 mg/kg-day of tris(chloropropyl)phosphate, which is described by the study authors as a mixture of the following four products: tris(1-chloromethylethyl)phosphate (a synonym for TCPP), bis(1-chloromethyl)(2-chloropropyl)phosphate, bis(2-chloropropyl)(1-chloromethyl)phosphate, and tris(2-chloropropyl)phosphate (relative abundance of each chemical species was not indicated)—in olive oil, presumably via gavage, for seven consecutive days (see Table 3B). Animals were monitored for changes in body weight and general signs of distress during the exposure (frequency not indicated), and body weight and organ weights were recorded on necropsy at Day 7. There were no significant differences in body weight. There were no abnormal clinical signs observed, but one 1000-mg/kg-day rat died. Only relative organ weights were presented. Relative liver weights were stated to be statistically significantly increased above the control in the 1000-mg/kg-day group by just under 10% (i.e., 9.7%). The study authors report a statistically significant increase in relative kidney weight in the 200- and 1000-mg/kg-day groups, however the data table indicates that the 40-mg/kg-day group is also statistically significantly higher than controls. Increases ranged from 9.8−20% but were not dose dependent, and the highest dose (i.e., 1000 mg/kg-day) was increased by less than 10% (i.e., 9.8%). The type of statistical analysis performed was not specified. There was no histopathology conducted; therefore, the significance of the organ-weight changes cannot be evaluated. The study authors did not provide a NOAEL. However a NOAEL of 8 mg/kg-day and a LOAEL of 40 mg/kg-day are determined from the data, based on the increase in relative kidney weight.

Bayer, 1993

Bayer (1993) provides another short-term study in rats. The original source (Bayer, 1993) was in German and is proprietary (not peer reviewed). EPA had the document translated on December 30, 2010. The study was stated not to be subject to GLP guidelines but was stated to generally be conducted in compliance with GLP guidelines with the exception that it was not examined by the quality assurance department. The study was conducted as a dose-range study for use in what the study authors refer to as a subacute study. Male Wistar rats (5/treatment group) were administered 0, 1, 10, 100, or 1000 mg/kg-day of TCPP (purity reported to be 97.85%, but this includes all isomers) in peanut oil via gavage for seven consecutive days (see Table 3B). Animals were 9 weeks old at the start of the experiment in order to study possible treatment-related testicular effects. Animals were observed once or twice a day for mortality and clinical signs of toxicity. Body weight was measured at the start and end of the experiment. Food and water consumption were measured at the beginning and before the end of the experiment, and consumption over the 7 days was calculated. On Day 8 all animals were sacrificed with diethyl ether and necropsied. The testicles (paired) were the only organ weighed. No histopathology was performed. There were no significant differences in mortality, clinical signs of toxicity, body weight, or food consumption. Water consumption was significantly increased by 32% in the 1000-mg/kg-day group. Although absolute and relative testes weights were decreased by ≥10% in the 100-mg/kg-day group, this was due to small testes in one animal and was not considered biologically significant by the study authors. No other significant effects were noted. The NOAEL is considered to be 1000 mg/kg-day and no LOAEL can be determined.

Stauffer Chemical Company, 1980a

Stauffer (Stauffer Chemical Company, 1980a) conducted another short-term study in rats. The original source (Stauffer Chemical Company, 1980a) was unavailable for review at this time. This study was considered proprietary and could not be obtained from the owner. An OECD SIDS (OECD, 2000) provided a peer-reviewed summary of the data. CD rats (10/sex/treatment group) were administered via the diet for two weeks 0-, 4200-, 6600-, 10,600-, or 16,600-ppm Fyrol PCF, which was stated in the study description to contain 70 ± 5% TCPP and 22 ± 5% 2-chloropropanol phosphate. Average daily intakes of Fyrol PCF are estimated to be 0, 379, 595, 956, and 1498 mg/kg-day in males and 0, 423, 665, 1067, and 1672 mg/kg-day in females (based on average body weight [U.S. EPA, 1994b], and average daily food consumption [U.S. EPA, 1988]). Because the compound was stated to contain only 70% TCPP, this would be equivalent to average daily intakes of TCPP of 0, 265, 417, 669, and 1048 mg/kg-day in males and 0, 296, 465, 747, and 1170 mg/kg-day in females. The OECD SIDS document (OECD, 2000) states that the study was not conducted according to GLP. Animals were examined for clinical signs of toxicity, food consumption, body weight, hematology, clinical chemistry, cholinesterase, gross necropsy, and select organ weights and histopathology. However, specifics (including statistical analyses performed) were not provided in the OECD SIDS document (OECD, 2000) (see Table 3B).

There were no treatment-related clinical signs noted. There were no treatment-related effects observed in hematology, clinical chemistry, or cholinesterase activity. High-dose (1048 mg/kg-day) males had a significant decrease in body weight gain and food consumption at Week 1 (magnitude of changes were not specified in the study summary). It was not indicated if this only occurred at Week 1 or continued throughout the study. Increases in absolute and

relative liver weight were reported but were stated not to be accompanied by histopathological changes. OECD considered the NOAEL to be 10,600 ppm (i.e., 669 mg/kg-day) (OECD, 2000), based on significant reduction in weight gain and reduced food consumption at the higher dose (1048 mg/kg-day) in males. However, no data were provided, and there is no indication of the magnitude of increase that was observed.

Metabolism/Toxicokinetic Studies

After a single oral dose of 50 μmol/kg, the majority of radio-labeled TCPP was recovered in the urine (67.17%) followed by the feces (22.17%) and expired air (7.72%) (Minegishi et al., 1988) (see Table 3B). Although there were high levels of TCPP found in the kidneys, liver, and lung after 3 hours, the levels decreased rapidly and were associated with excretion of the chemical as opposed to bioaccumulation. Measurements of biliary excretion indicated that enterohepatic circulation occurs. Stauffer Chemical Company (1984) also found that TCPP was rapidly eliminated (89% in 72 hours) with the majority excreted in the urine and feces.

Mode-of-Action/Mechanistic Studies

No mode-of-action or mechanistic studies on TCPP were identified.

Immunotoxicity

No immunotoxicity studies on TCPP were identified.

Neurotoxicity

Neurotoxicity was evaluated in 18 white Leghorn hens (Sprague et al., 1981) (see Table 3B). Although the hens exhibited decreased body weight, ceased egg production, severe feather loss, and one death, there was no behavioral or histological evidence of neurotoxicity. A short-term study (Stauffer Chemical Company, 1980a) and a subchronic study (Freudenthal and Henrich, 1999) examined cholinesterase levels (details provided above in the "Short-term studies" and "Subchronic studies" sections) and found no effects after either 2 weeks (Stauffer Chemical Company, 1980a) or 90 days (Stauffer Chemical Company, 1981) of treatment.

The potential of several phosphate ester flame retardants, including TCPP, to induce developmental neurotoxicity was examined in vitro using PC12 cells (Dishaw et al., 2011). TCPP reduced cell number but not cell growth. Additionally, TCPP promoted emergence of a cholinergic phenotype—but not a dopaminergic phenotype—from undifferentiated cells. This tendency to skew neural differentiation may elicit neurodevelopmental changes that would not be observed in classic developmental assays.

Table 3A. Summary of Tris(1-chloro-2-propyl)phosphate Genotoxicity Studies

Endpoint	Test system	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	Ames preincubation or plate assay; *Salmonella typhimurium* strains TA 97, 97a, 98, 100, 102, 104, 1535, 1537, and/or 1538 in the presence or absence of S9.	1 mM 10 µmol/plate 5.0 µL/plate 333−2000 µg/plate 1.0 µL/plate	-	-	Stauffer Chemical Company specified the compound as Fyrol PCF, which is a trade name and is 70 ± 5% TCPP.	Follman and Wober (2006); Nakamura et al. (1979); Stauffer Chemical Company (1978a)[c]; Zeiger et al. (1992); Mehlman et al. (1980)[c]
SOS repair induction	ND	ND	ND	ND	ND	NA
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	A modified Ames assay with yeast (*Saccharomyces cereviseae*) incubated at 30°C without S9 activation and 37°C with activation for 3−5 d.	5.0 µL/plate	-	-	No gene mutations were observed. Compound was specified to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. DMSO was used as the vehicle.	Stauffer Chemical Company(1978a)[c]
Recombination induction	ND	ND	ND	ND	ND	NA
Chromosomal aberration	ND	ND	ND	ND	ND	NA
Chromosomal malsegregation	ND	ND	ND	ND	ND	NA
Mitotic arrest	ND	ND	ND	ND	ND	NA

Table 3A. Summary of Tris(1-chloro-2-propyl)phosphate Genotoxicity Studies

Endpoint	Test system	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammalian cells—in vitro						
Mutation	A mouse lymphoma mutation assay using a Fisher mouse lymphoma cell line derived from the15178Y thymidine kinase (TK) cell line.	0.48 µL/mL	-	-	TCPP did not induce forward mutations in this assay. Compound was specified to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. DMSO was used as the vehicle.	Stauffer Chemical Company(1978b)[c]
Mutation	A murine lymphoma mutagenesis assay with and without S9.	NR	-	+	Compound was stated to be Antiblaze 80 (trade name), which is 75 ± 10% TCPP. In the first activation, mutagenicity was evident at highest dose with no dose response. In the second activation, mutagenic dose response was observed at all doses. At the highest dose, mutation frequency was 18 times the negative controls.	Mobil Oil Corp. (1981)[c,d]
Mutation	A BALB/3T3 cell (mouse embryonic fibroblast cell line) transformation assay; 10^4 cells were cultured with TCPP for 72 h and incubated for 3−4 wk, stained, and scored.	0.039−0.312 µL/mL	±	NA	Compound was stated to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. Nondose-related increase in cell transformation was observed at 0.039−0.312 µL/mL (higher doses demonstrated cytotoxicity). Foci occurred at equal frequency indicating a possible solubility or kinetics issue.	Stauffer Chemical Company (1978c)[c]

Table 3A. Summary of Tris(1-chloro-2-propyl)phosphate Genotoxicity Studies

Endpoint	Test system	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Mutation	A BALB/3T3 cell (mouse embryonic fibroblast cell line) transformation assay; 10^4 cells were cultured with TCPP for 72 h and incubated for 3−4 wk, stained, and scored.	0.02−3.00 µL/mL	-	NA	Compound was stated to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. There was no morphological transformation of BALB/3T3 in this assay.	Stauffer Chemical Company (1978d; 1980b)[c]
Chromosomal aberrations	ND	ND	ND	ND	ND	NA
Sister chromatid exchange (SCE)	ND	ND	ND	ND	ND	NA
DNA damage	In a comet assay, 300,000 V79 hamster fibroblast cells were cultured for 2 d with test compound. Culture medium was then replaced by fresh medium and test substance (1 µM−1 mM). A final protein concentration of 2-mg S9 protein/mL incubation medium was obtained. Two experiments were performed with a 24-h incubation period.	1 mM	-	-	Induction of DNA strand breaks could not be detected neither in the presence nor in the absence of S9 mix.	Follman and Wober (2006)
DNA damage	In an initial unscheduled DNA synthesis (UDS) assay, human WI-38 cells blocked in G-phase were grown in medium containing TCPP (referred to as Fyrol PCF, a trade name) in DMSO at concentrations of 0.1, 0.5, 1, or 5 µL/mL with and without S9-mix from rat livers. Based on toxicity above 0.1 µL/mL, the second assay was performed using concentrations of 0.005, 0.01, 0.05, and 0.1 µL/mL.	0.01 µL/mL	±	±	Test substance (Fyrol PCF, a trade name, 70 ± 5% TCPP) demonstrated toxicity at all concentrations in the first study and was perhaps weakly active at 0.01 µL/mL with and without activation, though no associated dose response was detected at higher concentrations. Results were ambiguous and equivocal with and without activation.	Stauffer Report (1978e)[c]

Table 3A. Summary of Tris(1-chloro-2-propyl)phosphate Genotoxicity Studies

Endpoint	Test system	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
DNA adducts	ND	ND	ND	ND	ND	NA
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	In a rat bone marrow cytogenetics assay, groups of 24 male Sprague-Dawley rats were administered a single oral bolus dose of 0.011-, 0.04-, or 0.11-mL/kg TCPP (referred to as Fyrol PCF, a trade name). Three equally sized groups also received the same doses in subcutaneous injections for 5 consecutive days. Animals were sacrificed 6−48 h following the last dose, and chromosome spreads were prepared and analyzed for aberrations.	0.11 mL/kg	-	NA	Compound was stated to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. Mitotic index approximately equaled that of the negative control. Chromosome aberration frequency was not significantly different in TCPP-treated animals; therefore, TCPP is not clastogenic.	Stauffer Chemical Company (1978f)[c]
Sister chromatid exchange (SCE)	ND	ND	ND	ND	ND	NA
DNA damage	ND	ND	ND	ND	ND	NA
DNA adducts	ND	ND	ND	ND	ND	NA
Mouse biochemical or visible specific locus test	ND	ND	ND	ND	ND	NA
Dominant lethal	ND	ND	ND	ND	ND	NA
Genotoxicity studies in subcellular systems						
DNA binding	ND	ND	ND	ND	ND	NA

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, – = negative, T = cytotoxicity, NA = not applicable, ND = no data, NDr = Not determined, NR = Not reported, NR/Dr = Not reported by the study authors but determined from data.
[c]Information was obtained from OECD SID (OECD, 2000). The original data were not available.
[d]Although the OECD SIDS document (OECD, 2000) did not specify an author for this study, a memo from Albright and Wilson (1989) stated that the study was from Mobil but that the study was incomplete.

Table 3B. Other Tris(1-chloro-2-propyl)phosphate Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity other than oral/inhalation	ND	ND	ND	NA
Other toxicity studies (exposures other than oral or inhalation)	In a neutral red uptake assay, cytotoxicity of TCPP was evaluated in V79 hamster fibroblast cells. 15,000 cells per well were seeded in 200-µL culture medium and cultured for 24 h; cells were withdrawn and incubated for 24 h with TCPP (100 pM to 10 mM) in serum-free culture medium. After 24 h, culture medium was withdrawn and replaced with another containing 0.05-mg neutral red/mL, incubated for 3 h, after which medium was withdrawn again; cells were washed and fixed with 50% ethanol-1% acetic acid in aqua bidest. V79 cells were incubated in TCPP with and without S9-mix activation. Uptake of neutral red was determined photometrically.	Moderate toxicity >1 mM in the presence of S9 (activation). No cytotoxic effects detected up to concentrations of 10 mM in the absence of S9 (no activation).	Cytotoxic effects only occurred at relatively high concentrations and were only detected in this study in the presence of S9. The protein content was stated not to be impacted either in the presence or absence of S9 activation.	Follman and Wober (2006)

Table 3B. Other Tris(1-chloro-2-propyl)phosphate Studies

Test	Materials and Methods	Results	Conclusions	References
Other toxicity studies (exposures other than oral or inhalation)	In an Ishikawa cell assay, the activity of alkaline phosphatase was measured as a parameter for an estrogenic effect in estradiol sensitive human endometrial adenocarcinoma Ishikawa cells by TCPP. Ishikawa cells were cultured in medium without phenol red with 5% fetal calf serum and insulin-transferrin-selenium A-supplement. A total of 125,000 cells were seeded per plate and incubated with TCPP (10 nM−10 µM, in ethanol). After 72 h, cells were harvested, resuspended, and analyzed. Alkaline phosphatase was assayed by spectrometry of product formation by hydrolysis of *p*-nitrophenyl phosphate to *p*-nitrophenol. Estrogen receptor-mediated effects were confirmed with a recombinant yeast assay with GLAXO ERα yeasts. To test antiestrogenic TCPP potential, ERα yeasts were induced by estradiol and then treated with the test substances.	TCPP did not induce activity of alkaline phosphatase in contrast to the positive control (estradiol 1 µM). In the yeast assay, activity of β-galactosidase secreted from GLAXO ERα yeasts demonstrated an estrogenic effect. TCPP did not reduce the induction origination from estradiol.	TCPP does not show estrogenic or antiestrogenic potential.	Follman and Wober (2006)
Short-term studies	Tris(chloropropyl)phosphate (a mixture that includes TCPP) was administered to female Wistar rats (5/group) at doses of 0, 8, 40, 200, or 1000 mg/kg-d in olive oil, presumably via gavage for 7 d.	There were no changes in body weight. Relative liver weight was increased at 1000 mg/kg-d by 9.7%. Relative kidney weight was increased at ≥40 mg/kg-d by 9.8−20%, but level of increase was not dose dependent. No histopathology was performed.	NOAEL of 8 mg/kg-d and LOAEL of 40 mg/kg-d based on increased relative kidney weight.	Kawasaki et al. (1982)[a]

Table 3B. Other Tris(1-chloro-2-propyl)phosphate Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term studies	Male Wistar rats (5/group) were treated with TCPP (97.85% purity; all isomers included) via gavage at doses of 0, 1, 10, 100, or 1000 mg/kg-d for 7 d. Animals were 9 wk old at the start of the study. The only organ weighed was the testis.	There were no changes in mortality, clinical signs of toxicity, body weight, or food consumption. There was a decrease in absolute and relative testes weights at 100 mg/kg-d; however, this was attributed to small testes in one animal and is not considered dose related. There was also an increase in water consumption at 1000 mg/kg-d, but this change was not considered adverse.	NOAEL of 1000 mg/kg-d; no LOAEL available from the data.	Bayer (1993)
Short-term studies	CD rats (10/sex/group) were treated with Fyrol PCF via the diet. Average TCPP intakes from this exposure were estimated to be 0, 265, 417, 669, and 1048 in males and 0, 296, 465, 747, and 1170 in females. Animals were examined for clinical signs of toxicity, food consumption, body weight, hematology, clinical chemistry, cholinesterase, gross necropsy, and select organs were weighed and examined for histopathology.	Noted changes included decreased body weight gain and food consumption at 1048 mg/kg-d in males. Increased absolute and relative liver weights were also reported, but no doses were given.	Compound was stated to be Fyrol PCF (trade name), which is 70 ± 5% TCPP. NOAEL of 669 mg/kg-d and LOAEL of 1048 mg/kg-d based on decrease in weight gain and food consumption. Doses were adjusted for TCPP content.	Stauffer Chemical Company (1980a)[b]
Metabolism/ toxicokinetics	Test substance (TCPP) was labeled to produce ^{14}C-TCPP (1.16 g yield), purified by column chromatography (yield 227 mg), analyzed by TLC, and purity ascertained by GC (>99%). Male Wistar rats had their bile ducts cannulated. After recovery, animals received a single oral dose (50 µmol/kg), and then bile was collected and analyzed for radioactivity. At 3, 6, 12, 24, 72, and 168 h after administration, animals were sacrificed, and several organs and tissues were removed to determine radioactivity. Excretion half-life was computed. Protein binding was determined using S-9 fraction of rat liver and kidney.	Recovery in urine, feces, and expired air were 67.17 ± 2.66, 22.17 ± 1.17, and 7.72 ± 0.84%, respectively. 44.9% of the dose was excreted through the bile duct in 48 h. The biliary/fecal excretion ratio was 2.23 at 48 h. Tissue and blood distribution results showed TCPP radioactivity most present in the kidney, liver, and lung at 3 h (27.26 ± 7.48, 28.64 ± 4.38, and 9.37 ± 1.51%, respectively). Distribution in the kidney, liver, and lungs decreased by 12 h and continued to decrease along with all tissue types. Longest half-life observed was in adipose tissue.	Biliary/fecal excretion ratio suggests reabsorption of biliary metabolites from the GI tract suggesting enterohepatic circulation. High liver and kidney distribution ratios reflect excretion rather than accumulation.	Minegishi et al. (1988)

Table 3B. Other Tris(1-chloro-2-propyl)phosphate Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetics	2-mL/kg-bw Fyrol PCF (stated to be 70 ± 5% TCPP) containing 20 or 200 mg TCPP/kg-bw and 40 μCi ^{14}C-radiolabeled TCPP was administered to CD rats. In recovery phase animals, at least 5 animals/sex received oral doses of 200 mg/kg, and 5 males received 20 mg/kg by single oral or i.v. administration; urine, feces, and expired air were collected over 8 d. In plasma phase animals, blood samples, urine, and feces were collected from dosed animals over 8 d. Collections were analyzed for radioactivity and TCPP metabolites.	TCPP and metabolites were rapidly eliminated (89% by 72 h). Terminal (plasma) half-life was 48.7 ± 6.0 h. Biphasic elimination followed first order kinetics. Urine was the primary mode of excretion dependent on dose and route of administration. Total body burden (8 d) <1%. Identifiable metabolites were 75−78.5% of urinary and fecal radiocarbon.	TCPP does not bioaccumulate significantly and is rapidly excreted.	Stauffer Chemical Company (1984)[b]
Mode of action/ mechanistic	ND	ND	ND	NA
Immunotoxicity	ND	ND	ND	NA
Neurotoxicity	A group of 18 white Leghorn hens received an oral dose of 13.2 g-TCPP/kg-bw initially and 3 wk later. Animals were sacrificed 3 wk after second dose.	Decreased body weights and a death were observed. Egg production ceased after the first dose, and severe feather loss occurred. No behavioral or histological evidence of delayed neurotoxicity was observed.	Neurotoxicity was not observed.	Sprague et al. (1981)
Neurotoxicity	PC12 cells were treated with TCPP (50 μM) and murine nerve growth factor (to promote differentiation). Media was renewed every 48 h. Cell number and growth were assessed after a 4-day exposure, and cell differentiation (measured by enzyme activity) was assessed after a 6-day exposure.	Decreased cell number—but not cell—growth was observed. TCPP resulted in increased cholinergic differentiation but had no impact on dopaminergic differentiation.	Potential for developmental neurotoxicity was observed.	Dishaw et al. (2011)

[a]This was published in a foreign journal, but a translation was provided by the National Institute of Health Science (NIHS, 1994).
[b]Information was obtained from an OECD SID document (OECD, 2000). The original data were not available.
NA = not applicable, ND = no data.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

Table 4 provides a summary of the relevant oral toxicity studies for TCPP. There are two subchronic studies: one in mice and one in rats (Freudenthal and Henrich, 1999; NTP, 2011a,b), and one developmental study in rats (Kawasaki et al., 1982) available that examine the effects of oral exposure to TCPP. The study by Kawasaki et al. (1982) uses a tris(chloropropyl)phosphate mixture; while TCPP is stated to be a component of the mixture, the relative abundance of TCPP to the other species in the mixture and the contributions of those other species to any observed toxicity are unknown, rendering the developmental studies by Kawasaki et al. (1982) unsuitable for derivation of RfD values. The subchronic study by Freudenthal and Henrich (1999) utilized a formulation that was only 70% TCPP. Information on the toxicological effects of the other major chemical component noted by the study authors (2-chloropropanol phosphate) could not be identified. It is unknown to what extent this chemical or others in the mixture may have contributed to the observed toxicity. In this review, doses were corrected for the TCPP content; however, this correction requires the assumption that the other chemicals in the mixture did not contribute to the observed effects. This assumption may be overly conservative. This study is not deemed suitable for derivation of quantitative toxicity values due to the uncertainties associated with the low purity of TCPP used. The subchronic study by NTP (2011a,b), used TCPP that was 95.7% pure and conducted a comprehensive evaluation of appropriate endpoints. However, at the time that this review was prepared, the study was unpublished and only the study abstract, summary tables, and complete data tables for mortality and body weight could be obtained. For these reasons, a provisional subchronic RfD cannot be confidently derived here. However a "screening level" value for subchronic oral exposure based on this study is provided in Appendix A.

Table 4. Summary of Relevant Oral Systemic Toxicity Studies for Tris(1-chloro-2-propyl)phosphate

References	Species, #Sex (M/F)	Exposure (ppm)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-d)	$LOAEL_{ADJ}$[b] (mg/kg-d)	Critical endpoint
Freudenthal and Henrich (1999)	Rat, 20/20	0, 800, 2500, 7500, or 20,000[c]	90 d	None	36	Increased absolute and relative liver weight in males
NTP (2011a,b)	Mouse, 10/10	0, 1250, 2500, 5000, 10,000, 20,000	14 wk	219	456	Increased relative liver weight and decreased terminal body weight in males
Kawasaki et al. (1982)	Rat, 0/11−14	0, 100, 1000, or 10,000[d]	20 d	69	670	Missing 13th rib in fetuses

[a]$NOAEL_{ADJ}$ = NOAEL (ppm or mg/kg food) × food consumption (kg/day) ÷ body weight (kg).
[b]$LOAEL_{ADJ}$ = LOAEL (ppm or mg/kg food) × food consumption (kg/day) ÷ body weight (kg).
[c]Compound used was only 70% TCPP; NOAEL and LOAEL values were adjusted to account for this.
[d]Compound used was tris(chloropropyl)phosphate, a mixture that contains TCPP. Doses are not adjusted for TCPP content, as the exact make-up of the mixture is not known.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

There are no chronic studies available, so the best available study for deriving a chronic provisional RfD is the subchronic study by NTP (2011a,b). However, as described above in the "Derivation of Subchronic Provisional RfD (Subchronic p-RfD)" section, due to the unavailability of the full study report at this time, a chronic provisional RfD cannot be confidently derived here. However a "screening level" value for chronic oral exposure is provided in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic p-RfC can be derived because no inhalation studies with TCPP were identified.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 5 identifies the cancer WOE descriptor for TCPP.

Table 5. Cancer WOE Descriptor for TCPP

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"		NA	
"Likely to Be Carcinogenic to Humans"		NA	
"Suggestive Evidence of Carcinogenic Potential"		NA	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is inadequate human and animal evidence of carcinogenicity via the oral or inhalation route.**
"Not Likely to Be Carcinogenic to Humans"		NA	

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Table 5 identifies the cancer WOE descriptor for both oral and inhalation exposure to TCPP as "*Inadequate Information to Assess Carcinogenic Potential*." Consequently, the lack of data on the carcinogenicity of TCPP precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure. However, at the time that this review was prepared, a chronic carcinogenicity study using TCPP in the diet was planned by NTP (study number C20712).

Tables 6 and 7 present a summary of noncancer and cancer values, respectively.

Table 6. Summary of Noncancer Reference Values for TCPP (CASRN 13674-84-5)

Toxicity Type (units)	Species/Sex	Critical Effect	Provisional Reference Value	POD Method	POD	UF_C	Principal Study
Screening Subchronic p-RfD (mg/kg-d)	Mouse/M	Increase in incidence of hepatocyte hypertrophy	1×10^{-1}	$BMDL_{10}$	138	1000	NTP (2011a,b)
Screening Chronic p-RfD (mg/kg-d)	Mouse/M	Increase in incidence of hepatocyte hypertrophy	1×10^{-2}	$BMDL_{10}$	138	10,000	NTP (2011a,b)
Subchronic p-RfC (mg/m^3)	None	None	None	None	None	None	None
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

Table 7. Summary of Cancer Values for TCPP (CASRN 13674-84-5)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive a provisional chronic p-RfD for tris(1-chloro-2-propyl)phosphate (TCPP). However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

Derivation of Screening Subchronic Provisional RfD (Screening Subchronic p-RfD)

As discussed in the "Derivation of Subchronic Provisional RfD (Subchronic p-RfD)" section, the subchronic study in mice by NTP (2011a,b) is chosen as the principal study. A LOAEL of 456 mg/kg-day was identified based on increased relative liver weight and decreased terminal body weight in male mice; a NOAEL of 219 was also identified in this study. Liver histopathology was also observed, with a statistically significantly increased incidence of hepatocyte hypertrophy in male mice at ≥2470 mg/kg-day and in female mice at ≥906 mg/kg-day (NTP, 2011a). Benchmark dose (BMD) modeling was performed on the data to determine the most appropriate POD. Details of the modeling results are provided in Appendix C. While the lowest NOAELs from the NTP (2011a,b) study were for terminal body weight and relative liver weight in male mice (219 mg/kg-day), the data for these endpoints could not be modeled, and a lower $BMDL_{10}$ is available based on hepatocyte hypertrophy in male mice (see Table A.1). The most sensitive effect was hepatocyte hypertrophy in male mice with a BMD_{10} of 310 mg/kg-day and a $BMDL_{10}$ of 138 mg/kg-day. Further support for the induction of liver effects by TCPP is provided by short-term studies (Kawasaki et al., 1982; Stauffer Chemical Company, 1980a) in which increased liver weight was observed, and by the subchronic study using Fyrol PCF (Freudenthal and Henrich, 1999) in which increased liver weight and increased incidence of swelling around the periportal hepatocytes were observed.

Table A.1. Potential Points of Departure (mg/kg-day) Available from NTP (2011a,b) Study				
Endpoint	**NOAEL**	**LOAEL**	**BMD_{10}**	**$BMDL_{10}$**
Terminal body weight	M: 219 F: 1830	M: 456 F: 3590	M: N/A F: N/A	M: N/A F: N/A
Relative liver weight	M: 219 F: 420	M: 456 F: 906	M: N/A F: N/A	M: N/A F: N/A
Hepatocyte hypertrophy*	**M: 737 F: 420**	**M: 2470 F: 906**	**M: 310 F: 802**	**M: 138 F: 470**
Hematology	M: 737 F: 1830	M: 2470 F: 3590	M: N/A F: N/A	M: N/A F: N/A
Mortality	M: 4410 F: 3590	M: N/A F: N/A	M: N/A F: N/A	M: N/A F: N/A

*NOAEL and LOAEL values for hepatocyte hypertrophy are based on statistically significant ($p < 0.05$) changes in incidence of hypertrophy according to a Fisher's Exact Test performed for this review.

The POD identified in this study is a $BMDL_{10}$ of 138 mg/kg-day.

This POD was derived using doses adjusted from ppm in the diet to mg/kg-day using average food consumption and body-weight measurements provided in the study (see "Review of Potentially Relevant Data" section for details).

The screening subchronic p-RfD for TCPP, based on the $BMDL_{10}$ of 138 mg/kg-day for hepatocyte hypertrophy in male mice, is derived as follows:

$$\textbf{Screening subchronic p-RfD} = BMDL_{10} \div UF$$
$$= 138 \text{ mg/kg-day} \div 1000$$
$$= \mathbf{1 \times 10^{-1} \text{ mg/kg-day}}$$

Table A.2 summarizes the uncertainty factors for the screening subchronic p-RfD for TCPP.

Table A.2. Uncertainty Factors for Screening Subchronic p-RfD of TCPP		
UF	**Value**	**Justification**
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between mice and humans.
UF_D	10	A UF_D of 10 is applied because the database includes only one unacceptable developmental study in Wistar rats (Kawasaki et al., 1982b) and no two-generation reproduction studies. Additionally, there is information suggesting the need for more studies addressing the developmental neurotoxicity of TCPP (Dishaw et al., 2011).
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a $BMDL_{10}$.
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized.
$UF_C \leq 3000$	1000	

Derivation of Screening Chronic Provisional RfD (Screening Chronic p-RfD)

There are no available chronic studies using TCPP. The study by NTP (2011a,b) is selected as the principal study for derivation of the screening chronic p-RfD. The critical endpoint is increased incidence of hepatocyte hypertrophy in male mice. Details of the principal study (NTP, 2011a,b) are provided in the "Review of Potentially Relevant Data" section. Benchmark dose (BMD) analysis was performed with these data and is described in Appendix C.

The POD identified in this study is a $BMDL_{10}$ of 138 mg/kg-day.

This POD was derived using doses adjusted from ppm in the diet to mg/kg-day using average food consumption and body weight measurements provided in the study (see "Review of Potentially Relevant Data" section for details). No animal-to-human body weight adjustment is used for oral noncancer assessments.

The screening chronic p-RfD for TCPP, based on the $BMDL_{10}$ of 138 mg/kg-day in male mice, is derived as follows:

$$\textbf{Screening Chronic p-RfD} = BMDL_{10} \div UF_C$$
$$= 138 \text{ mg/kg-day} \div 10{,}000$$
$$= \mathbf{1 \times 10^{-2} \text{ mg/kg-day}}$$

Table A.3 summarizes the uncertainty factors for the screening chronic p-RfD for TCPP.

Table A.3. Uncertainty Factors for Screening Chronic p-RfD for TCPP

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between mice and humans.
UF_D	10	A UF_D of 10 is applied because the database includes only one unacceptable developmental study in Wistar rats (Kawasaki et al., 1982b) and no two-generation reproduction studies. Additionally, there is information suggesting the need for more studies addressing the developmental neurotoxicity of TCPP (Dishaw et al., 2011).
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a $BMDL_{10}$.
UF_S	10	A UF_S of 10 is applied because a subchronic-duration study was utilized.
$UF_C \leq 3000$	10,000	

APPENDIX B. DATA TABLES

Table B.1. Effect of 13-Week TCPP Exposure on Rat Body Weight[a]

		ppm Fyrol PCF in diet (TCPP Adjusted Daily Dose to males, females in mg/kg-d)[b]				
		0	**800 (36, 43)**	**2500 (112, 120)**	**7500 (337, 399)**	**20,000 (944, 1222)**
Body weight (g)[c]	Male	490 ± 35	491 ± 39 (0.2)	477 ± 48 (2.7)	473 ± 49 (3.5)	452 ± 40 (7.8)[d]
	Female	263 ± 23	265 ± 25 (0.8)	264 ± 31 (0.4)	250 ± 22 (4.9)	232 ± 16 (11.8)[d]

[a]Source: Freudenthal and Henrich (1999).
[b]Adjusted Daily Dose was calculated from the average daily Fyrol PCF consumption reported by the study authors for each dose group and is adjusted to account for the 70% TCPP content of Fyrol PCF.
[c]Mean ± SD (% change from control).
[d]$p < 0.05$ compared to control.

Table B.2. Changes in Organ Weights Following 13-Week TCPP Treatment in CD Rats[a]

		ppm Fyrol PCF in diet (TCPP Adjusted Daily Dose to males, females in mg/kg-d)[b]				
		0	**800 (36, 43)**	**2500 (112, 120)**	**7500 (337, 399)**	**20,000 (944, 1222)**
Absolute liver weight (g)[c]	Male	11.78 ± 1.04	13.65 ± 1.87 (16)[d]	13.99 ± 1.93 (19)[d]	13.56 ± 1.76 (15)[d]	15.47 ± 2.34 (31)[d]
	Female	6.63 ± 0.84	6.93 ± 0.87 (4.5)	6.99 ± 0.81 (5.4)	7.77 ± 1.21 (17)[d]	7.74 ± 0.95 (17)[d]
Relative liver weight (g)[c]	Male	24.06 ± 1.73	27.82 ± 3.42 (16)[d]	29.37 ± 3.38 (22)[d]	28.63 ± 1.72 (19)[d]	34.08 ± 2.99 (42)[d]
	Female	25.15 ± 2.25	26.1 ± 2.08 (3.7)	26.57 ±1.65 (5.6)	31.04 ± 4.09 (23)[d]	33.45 ± 5.00 (33)[d]
Relative kidney weight (g)[c]	Male	5.63 ± 0.56	5.82 ± 0.42 (3.4)	6.19 ± 0.59 (9.9)	6.37 ± 0.49 (13)[d]	6.54 ± 0.60 (16)[d]
	Female	6.51 ± 0.72	6.45 ± 0.58 (0.9)	6.27 ± 0.65 (3.7)	6.65 ± 0.61 (2.2)	7.06 ± 1.18 (8.4)

[a]Source: Freudenthal and Henrich (1999).
[b]Adjusted Daily Dose was calculated from the average daily Fyrol PCF consumption reported by the study authors for each dose group and is adjusted to account for the 70% TCPP content of Fyrol PCF.
[c]Mean ± SD (% change from control).
[d]$p < 0.05$ compared to control.

Table B.3. Histopathological Changes Following 13-Week TCPP Treatment in CD Rats[a]

		ppm Fyrol PCF in diet (TCPP Adjusted Daily Dose to males, females in mg/kg-d)[b]				
		0	**800 (36, 43)**	**2500 (112, 120)**	**7500 (337, 399)**	**20,000 (944, 1222)**
Thyroid follicular hyperplasia	Male	5	5	3	10	8
	Female	0	2	2	9	5
Liver periportal swelling	Male	0	0	0	0	9
	Female	5	0	0	0	8
Renal cortical tubular degeneration	Male	0	0	0	13	7
	Female	1	0	0	0	4

[a]Source: Freudenthal and Henrich (1999).
[b]Adjusted Daily Dose was calculated from the average daily Fyrol PCF consumption reported by the study authors for each dose group and is adjusted to account for the 70% TCPP content of Fyrol PCF.

Table B.4. Average Body Weight[a] in Male Mice Exposed to TCPP in the Diet for 14 Weeks[b]

TCPP[c]	Weeks on Study													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	21.7 ± 1.1	23.3 ± 1.0	24.0 ± 1.8	25.0 ± 1.1	25.4 ± 1.2	27.1 ± 1.6	27.8 ± 2.0	28.9 ± 2.2	29.6 ± 2.5	30.9 ± 2.6	31.5 ± 2.8	32.4 ± 3.5	32.6 ± 3.8	33.3 ± 3.9
1250 (219)	21.9 ± 0.9 (+0.9)	23.1 ± 0.8 (−0.6)	24.0 ± 0.9 (0)	24.9 ± 1.1 (−0.4)	25.6 ± 1.6 (+0.7)	26.6 ± 1.7 (−1.8)	27.3 ± 1.8 (−1.5)	28.5 ± 2.0 (−1.5)	28.9 ± 2.2 (−2.3)	29.4 ± 1.6 (−4.8)	29.8 ± 1.9 (−5.3)	30.9 ± 2.1 (−4.6)	31.2 ± 2.2 (−4.5)	32.0 ± 2.1 (−3.9)
2500 (456)	21.8 ± 0.9 (+0.6)	22.9 ± 0.9 (−1.5)	23.7 ± 0.9 (−1.1)	24.6 ± 0.8 (−1.6)	25.2 ± 1.0 (−0.9)	25.7 ± 1.2 (−5.3)	26.4 ± 1.4 (−4.9)	27.5 ± 1.3 (−5.0)	27.5 ± 1.4 (−7.1)	27.5 ± 3.0 (−11.1)*	28.4 ± 2.0 (−9.7)	29.1 ± 2.3 (−10.0)	29.1 ± 2.1 (−10.9)	29.7 ± 2.4 (−10.7)*
5000 (737)	21.9 ± 0.8 (+0.9)	22.3 ± 1.0 (−4.2)	23.1 ± 1.0 (−3.7)	23.6 ± 0.9 (−5.4)*	24.0 ± 1.1 (−5.6)*	24.7 ± 1.0 (−8.9)*	25.4 ± 1.0 (−8.5)*	25.9 ± 0.9 (−10.4)	26.2 ± 1.0 (−11.4)*	26.7 ± 1.0 (−13.4)*	26.8 ± 0.8 (−14.9)*	27.9 ± 1.1 (−13.9)*	27.5 ± 1.0 (−15.7)*	27.9 ± 1.2 (−16.1)*
10,000 (2470)	21.2 ± 0.9 (−2.0)	21.7 ± 0.6 (−6.9)*	22.3 ± 0.5 (−7.0)*	22.8 ± 0.5 (−8.9)*	22.9 ± 0.5 (−9.7)*	23.9 ± 0.9 (−11.9)*	24.2 ± 0.6 (−12.8)*	24.8 ± 0.7 (−14.3)*	25.0 ± 0.7 (−15.6)*	24.0 ± 2.7 (−22.2)*	25.1 ± 1.0 (−20.2)*	25.9 ± 1.3 (−20.1)*	25.6 ± 1.1 (−21.6)*	25.3 ± 2.8 (−24.2)*
20,000 (4410)	20.2 ± 0.7 (−6.6)*	20.1 ± 1.7 (−13.5)*	21.0 ± 0.8 (−12.3)*	21.5 ± 0.6 (−14.1)*	21.8 ± 0.9 (−14.1)*	22.1 ± 0.7 (−18.2)*	22.7 ± 0.8 (−18.1)*	23.4 ± 0.8 (−19.2)*	23.3 ± 0.9 (−21.2)*	23.9 ± 0.9 (−22.6)*	24.0 ± 0.8 (−23.7)*	25.0 ± 0.9 (−22.8)*	24.4 ± 1.0 (−25.2)	23.8 ± 2.5 (−28.7)*

[a]Average body weight expressed as mean ± SD in g (% change from control).
[b]Source: NTP (2011b).
[c]TCPP dose expressed as ppm in feed (mg/kg-day).
*Significantly different from control at $p < 0.05$ based on ANOVA and subsequent Dunnett's test performed for this review.

Table B.5. Average Body Weight[a] in Female Mice Exposed to TCPP in the Diet for 14 Weeks[b]

TCPP[c]	Weeks on Study													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	17.7 ± 1.1	18.8 ± 0.9	19.8 ± 1.1	20.4 ± 0.7	20.6 ± 0.8	21.8 ± 1.1	21.8 ±1.0	22.2 ± 0.8	23.3 ± 0.9	24.4 ± 0.7	23.4 ± 1.5	24.0 ± 1.2	24.6 ± (1.0)	24.5 ± 1.0
1250 (198)	17.7 ± 0.8 (0)	18.8 ± 0.6 (0)	19.5 ± 0.7 (−1.9)	20.4 ± 0.9 (0)	20.6 ± 0.7 (0)	21.7 ± 0.5 (−0.5)	22.4 ± 0.7 (+2.6)	22.8 ± 0.6 (+3.0)	24.1 ± 0.8 (+3.3)	24.7 ± 0.8 (+1.1)	24.9 ± 1.0 (+6.5)	24.7 ± 0.9 (+2.6)	25.3 ± 0.7 (+2.7)	21.6 ± 0.5 (−12)*
2500 (420)	17.7 ± 0.6 (0)	14.6 ± 0.8 (−22.1)*	19.0 ± 0.9 (−4.4)	19.7 ± 0.8 (−3.2)	20.2 ± 0.5 (−1.6)	21.6 ± 0.8 (−1.0)	22.0 ± 0.8 (+0.9)	22.0 ± 0.8 (−0.8)	23.2 ± 0.8 (−0.7)	24.0 ± 0.9 (−1.6)	24.5 ± 0.8 (+4.7)	24.0 ± 0.8 (0)	25.0 ± 0.8 (+1.4)	22.7 ± 3.0 (−7.5)
5000 (906)	17.4 ± 1.0 (−2.1)	16.6 ± 1.8 (−11.7)*	18.6 ± 1.0 (−6.3)*	19.5 ± 1.2 (−4.4)	19.9 ± 0.9 (−3.4)	20.8 ± 1.1 (−4.8)*	21.4 ± 1.3 (−1.9)	21.5 ± 0.9 (−3.2)	22.2 ± 0.8 (−5.0)*	23.1 ± 1.0 (−5.3)*	23.1 ± 0.9 (−1.2)	22.8 ± 1.2 (−5.2)*	23.4 ± 1.2 (−5.2)*	23.8 ± 1.1 (−2.9)
10,000 (1930)	17.3 ± 0.7 (−2.6)	17.7 ± 0.6 (−5.7)	18.0 ± 0.7 (−9.1)*	18.6 ± 0.6 (−8.7)*	19.0 ± 0.8 (−7.8)*	19.9 ± 0.8 (−8.9)*	20.1 ± 0.9 (−7.8)*	20.5 ± 0.9 (−7.5)*	21.1 ± 0.7 (−9.6)*	22.1 ± 1.0 (−9.4)*	22.2 ± 1.0 (−5.1)*	21.7 ± 0.9 (−9.5)*	22.2 ± 1.3 (−9.9)*	22.2 ± 1.4 (−9.5)*
20,000 (3590)	16.2 ± 1.0 (−8.6)*	17.3 ± 0.8 (−8.0)*	17.7 ± 0.8 (−10.9)*	17.8 ± 0.9 (−12.6)*	18.1 ± 0.8 (−11.8)*	18.8 ± 1.0 (−13.7)*	18.8 ± 0.8 (−13.8)*	18.8 ± 1.1 (−15.2)*	19.8 ± 0.8 (−15.3)*	20.4 ± 0.9 (−16.5)*	20.5 ± 1.0 (−12.3)*	20.5 ± 1.0 (−14.7)	19.9 ± 1.1 (−19.4)*	20.8 ± 1.0 (−15.2)*

[a]Average body weight expressed as mean ± SD in g (% change from control).
[b]Source: NTP (2011b).
[c]TCPP dose expressed as ppm in feed (mg/kg-day); dose adjusted using food consumption and body weight data reported in the study.
*Significantly different from control at $p < 0.05$ based on ANOVA and subsequent Dunnett's test performed for this review.

Table B.6. Food Consumption, Liver Weight Change, and Hepatocyte Hypertrophy in Mice Treated with TCPP in the Diet for 14 Weeks[a]

	TCPP dose (ppm in diet [mg/kg-d])[b]					
Males	**0**	**1250 (219)**	**2500 (456)**	**5000 (737)**	**10,000 (2470)**	**20,000 (4410)**
Mean daily food consumption (g [% change from control])	4.6	4.8 (4)	4.8 (4)	5.2 (13)	5.9 (28)	5.0 (9)
Relative liver weight (% change from control)	N/A	5[c]	11[c]	21[c]	40[c]	94[c]
Hepatocyte hypertrophy (# affected/total)	0/10	0/10	3/10	4/10	10/10[d]	10/10[d]
	TCPP dose (ppm in diet [mg/kg-d])[b]					
Females	**0**	**1250 (198)**	**2500 (420)**	**5000 (906)**	**10,000 (1930)**	**20,000 (3590)**
Mean daily food consumption (g [% change from control])	3.3	3.5 (6)	3.6 (9)	3.8 (15)	3.7 (12)	3.4 (3)
Relative liver weight (% change from control)	N/A	4[c]	6	11[c]	19[c]	47[c]
Hepatocyte hypertrophy (# affected/total)	0/10	0/10	0/10	5/10[d]	10/10[d]	10/10[d]

[a]Source: NTP (2011a).
[b]Dose adjusted using food consumption and body weight data reported in the study.
[c]Statistically different from control at $p \leq 0.05$ as reported by study authors.
[d]Statistically different from control at $p \leq 0.05$ based on Fisher's Exact test performed for this review.
N/A: Not Applicable.

APPENDIX C. BMD OUTPUTS

MODEL-FITTING PROCEDURE FOR QUANTAL NONCANCER DATA

The model-fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA BMDS (version 2.1) are fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest BMDL is selected as the POD when the difference between the BMDLs estimated from these models is more than 3-fold (unless it is an outlier); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. In accordance with EPA (2000) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk are calculated for all models.

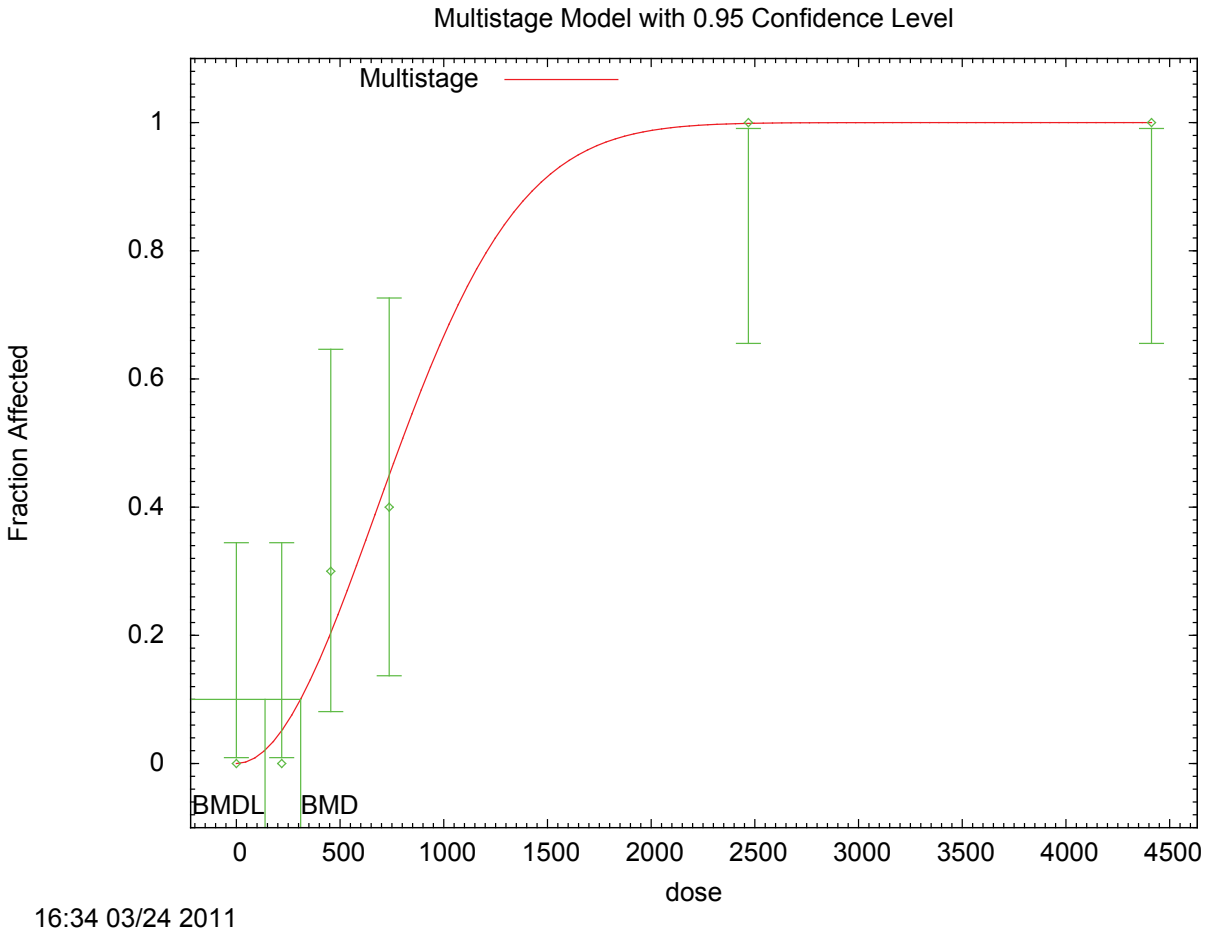
MODEL-FITTING RESULTS FOR HEPATOCYTE HYPERTROPHY IN MALE MICE (NTP, 2011a)

Applying the procedure outlined above to the data (see Table B.6) for hepatocyte hypertrophy in male mice exposed subchronically to TCPP via diet for 14 weeks (NTP, 2011a), all models provided adequate fit to the data (see Table C.1). However, the first-degree multistage model and the quantal-linear model provided poor fit in the low-dose region and were excluded from consideration. Of the remaining models, the $BMDL_{10}$s differed by less than 3-fold, so the model with the lowest AIC (second-degree multistage) was selected. The BMD_{10} and $BMDL_{10}$ for hepatocyte hypertrophy in male mice were 310 and 138 mg/kg-day, respectively. Figure C.1 shows the fit of the second degree multistage model to the data.

Table C.1. Model Predictions for the Incidence of Hepatocyte Hypertrophy in Male Mice Treated with TCPP in the Diet for 14 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	4	1.31	0.8593	31.2323	345.328	177.454
Logistic	4	2.3	0.6813	32.4306	380.604	252.026
Log-Logistic[c]	4	1.84	0.7647	31.858	363.451	220.08
Log-Probit[c]	4	1.44	0.8367	31.3251	360.007	225.345
Multistage (degree = 1)[d]	5	3.92	0.5611	34.6386	117.803	79.3911
Multistage (degree = 2)[d]	***5***	***1.22***	***0.9425***	***29.3711***	***310.099***	***138.32***
Multistage (degree = 3)[d]	4	1.25	0.8691	31.3627	315.472	123.483
Multistage (degree = 4)[d]	3	1.25	0.7419	33.3613	314.203	118.179
Multistage (degree = 5)[d]	4	1.23	0.8726	31.3542	312.626	116.479
Probit	4	1.99	0.738	32.0008	366.693	238.462
Weibull[b]	4	1.3	0.8612	31.3404	326.299	161.844
Quantal-Linear	5	3.92	0.5611	34.6386	117.803	79.3911

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD.



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week).

Figure C.1. Fit of Multistage (degree = 2) Model to Data on Hepatocyte Hypertrophy in Male Mice Treated with TCPP in the Diet for 14 Weeks

MODEL-FITTING RESULTS FOR HEPATOCYTE HYPERTROPHY IN FEMALE MICE (NTP, 2011a)

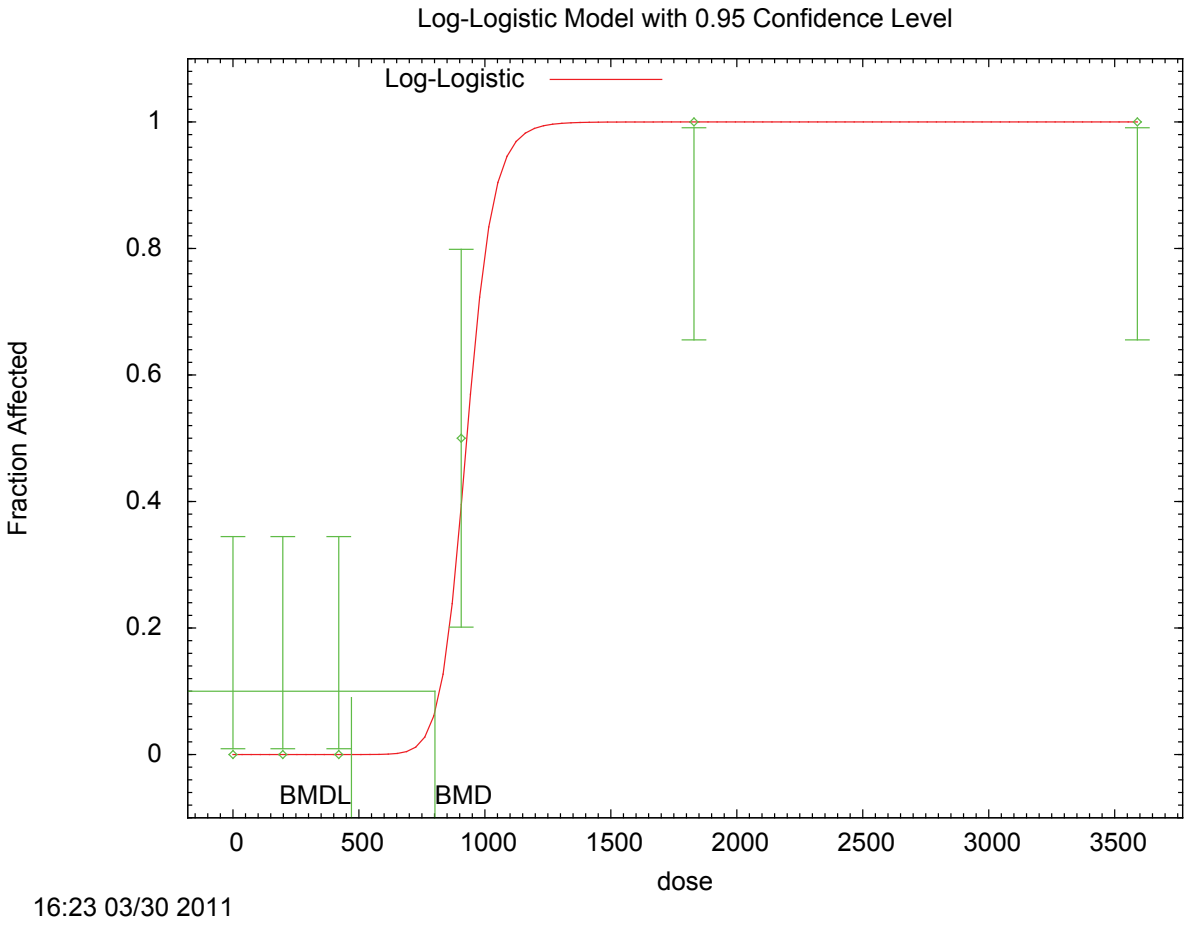
Applying the procedure outlined above to the data (see Table B.6) for hepatocyte hypertrophy in female mice exposed subchronically to TCPP via the diet for 14 weeks (NTP, 2011a), all models provided adequate fit to the data except for the first-degree multistage model, the Weibull model, and the quantal-linear model (see Table C.2). Of the remaining models, the $BMDL_{10}$s differed by less than 3-fold, so the model with the lowest AIC (log-logistic) was selected. The BMD_{10} and $BMDL_{10}$ for hepatocyte hypertrophy in female mice were 802 and 470 mg/kg-day, respectively. Figure C.2 shows the fit of the log-logistic model to the data.

Table C.2. Model Predictions for the Incidence of Hepatocyte Hypertrophy in Female Mice Treated with TCPP in the Diet for 14 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	5	0.02	1	15.9118	658.262	432.104
Logistic	4	0	1	17.8629	849.083	473.396
Log-Logistic[c]	***5***	***0***	***1***	***15.863***	***801.89***	***470.386***
Log-Probit[c]	4	0	1	17.8629	773.617	451.846
Multistage (degree = 1)[d]	5	9.34	0.0961	32.1341	124.7	85.3798
Multistage (degree = 2)[d]	5	2.57	0.7658	20.7235	353.942	243.55
Multistage (degree = 3)[d]	5	0.81	0.9764	17.4037	498.207	335.397
Multistage (degree = 4)[d]	5	0.34	0.9968	16.5128	575.256	375.808
Multistage (degree = 5)[d]	4	0.32	0.9888	18.4686	581.405	373.335
Probit	4	0	1	17.8629	795.498	440.581
Weibull[be]				13.8644		
Quantal-Linear	5	9.34	0.0961	32.1341	124.7	85.3798

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Model failed to reach convergence in the allowed number of iterations (250).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD.



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week).

Figure C.2. Fit of Log-logistic Model to Data on Hepatocyte Hypertrophy in Female Mice Treated with TCPP in the Diet for 14 Weeks

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA

The model-fitting procedure for continuous data is as follows. The simplest model (linear) in the EPA's BMD software (BMDS version 2.1.2) is first applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then all of the available models are fit to the data while assuming constant variance. Among the models providing adequate fit to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the models are run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then a model is chosen for BMD derivation based on adequate fit to the means ($p \geq 0.1$) and lowest AIC. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered unsuitable for modeling.

MODEL-FITTING RESULTS FOR TERMINAL BODY WEIGHT IN MALE MICE (NTP, 2011b)

Applying the procedure outlined above to the data (see Table B.4) for terminal body weight in male mice exposed subchronically to TCPP via the diet for 14 weeks (NTP, 2011b), the variance was nonhomogenous and could not be modeled using the Power model in the BMD software (see Table C.3). Therefore, these data are unsuitable for modeling. However, terminal body weight and relative liver weight in male mice (which was also unsuitable for modeling due to lack of means and standard deviations in data reporting) provided the lowest LOAEL and NOAEL for the NTP (2011a,b) study. These values were 456 and 219 mg/kg-day, respectively. BMD modeling of the incidence of hepatocyte hypertrophy was possible, and the $BMDL_{10}$ (138 mg/kg-day) was lower than the NOAEL for liver and body weights. While the variance models did not fit for terminal body weight in male mice, three models provide adequate fit to the means (4^{th} and 5^{th} degree exponential models and the Hill model). Comparing the BMD_{10}s from these models (389−419 mg/kg-day) to the BMD_{10} for hepatocyte hypertrophy in males (310 mg/kg-day) confirms that hepatocyte hypertrophy is a more sensitive effect than decreased terminal body weight and, therefore, is an appropriate POD.

Table C.3. Model Predictions for Terminal Body Weight in Male Mice Treated with TCPP in the Diet for 14 Weeks[a]					
Model	**Variance *p*-Value[b]**	**Means *p*-Value[b]**	**AIC**	**BMD_{10} (mg/kg-d)**	**$BMDL_{10}$ (mg/kg-d)**
Constant variance					
Exponential (degree = 2)	0.02296	0.004434	189.9877	1409.6	1164.08
Exponential (degree = 3)	0.02296	0.004434	189.9877	1409.6	1164.08
Exponential (degree = 4)	*0.02296*	*0.6846*	*178.345*	*407.283*	*266.856*
Exponential (degree = 5)	*0.02296*	*0.6846*	*178.345*	*407.283*	*266.856*
Hill[c]	*0.02296*	*0.6892*	*179.599717*	*419.41*	*244.768*
Linear[d]	0.02296	0.001763	192.06049	1603.47	1358.42
Polynomial[c]	0.02296	0.001763	192.06049	1603.47	1358.42
Power[c]	0.02296	0.001763	192.06049	1603.47	1358.42
Modeled variance					
Exponential (degree = 2)	0.01867	0.003127	191.5604	1455.97	1177.79
Exponential (degree = 3)	0.01867	0.003127	191.5604	1455.97	1177.79
Exponential (degree = 4)	*0.01867*	*0.6247*	*179.3946*	*389.155*	*245.682*
Exponential (degree = 5)	*0.01867*	*0.6247*	*179.3946*	*389.155*	*245.682*
Hill[c]	*0.01867*	*0.6216*	*180.590222*	*390.25*	*241.934*
Linear[d]	0.01867	0.00126	193.593512	1651.91	1373.53
Polynomial[c]	0.01867	0.00126	193.593512	1651.91	1373.53
Power[c]	0.01867	0.00126	193.593512	1651.91	1373.53

[a]NTP (2011b).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Coefficients restricted to be positive.

MODEL-FITTING RESULTS FOR TERMINAL BODY WEIGHT IN FEMALE MICE (NTP, 2011b)

The data for terminal body weight in female mice cannot be modeled due to a nonmonotonic dose-response curve (see Table B.5).

APPENDIX D. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2011) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. As cited in HSDB (Hazardous Substances Data Bank). Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. Accessed on 9/12/2011. 783980

Albright and Wilson Americas. (1989) Eighteen health and safety studies on antiblaze 80 with cover letter dated 021389. Albright & Wilson Americas, Inc. Glen Allen, VA; Report No. TSCATS 311056 EPA/OTS Doc. # 86–890000114. OTS# 0517715. 659039

ATSDR (Agency for Toxic Substances and Disease Registry). (2009) Draft toxicological profile for phosphate ester flame retardants. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at http://www.atsdr.cdc.gov/toxprofiles/tp202.pdf. Accessed on 9/12/2011. 1325317

Bayer, AG. (1993) Tris-chloroisopropylphosphate, vorversuch zur dosisfindung fur eine subakute toxikologische studie an mannlichen wistar-ratten (in german) with cover letter dated 11/15/93. Germany, Report No. 86940000032. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0556628. Translation provided on December 30, 2010. 656603

CalEPA (California Environmental Protection Agency). (2008) All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of December 18, 2008. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html. Accessed on 9/12/2011. 595416

CalEPA (California Environmental Protection Agency). (2009) OEHHA toxicity criteria database. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/risk//ChemicalDB/index.asp. Accessed on 9/12/2011. 595417

Dishaw, LV; Powers, CM; Ryde, IT; et al. (2011) Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. *Toxicol Appl Pharmacol* In press. Doi:10.1016/j.taap.2011.01.005. 781782

Follmann, W; Wober, J. (2006) Investigation of cytotoxic, genotoxic, mutagenic, and estrogenic effects of the flame retardants tris-(2-chloroethyl)-phosphate (TCEP) and tris-(2-chloropropyl)-phosphate (TCPP) in vitro. *Toxicol Lett* 161:124−134. Available online at http://dx.doi.org/10.1016/j.toxlet.2005.08.008. 656597

Freudenthal, RI; Henrich, RT. (1999) A subchronic toxicity study of Fyrol PCF in Sprague-Dawley Rats. *Int J Toxicol* 18(3):173−176. 679695

IARC (International Agency for Research on Cancer). (2011) Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC. Available online at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php. Accessed on 9/12/2011. 783869

IPCS (International Programme for Chemical Safety). (1998) Flame retardants: Tris(chloropropyl) phosphate and tris(2-chloroethyl) phosphate. Environmental Health Criteria 209. Geneva: WHO. Available online at http://whqlibdoc.who.int/ehc/WHO_EHC_209.pdf. Accessed on 9/12/2011. 1325318

Kawasaki, H; et al. (1982) Studies on the toxicity of insecticides and food additives in pregnant rats-(5) foetal toxicity of tris-(chloropropyl) phosphate. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86-950000008. OTS0557521. Translation provided in NIHS (1994). 1325319

Mehlman, MA; Mackerer, CR; Schreiner, A. (1980) An Ames Salmonella/mammalian microsome mutagenesis assay for determination of potential mutagenecity of tris-(2-chloropropyl) phosphate. Mobil Environmental and Health Science Laboratory, Princeton, NJ, Report No. 471-80. As cited in OECD (2000). 656588

Minegishi, KI; Kurebayashi, H; Nambaru, S; et al. (1988) Comparative studies on absorption, distribution, and excretion of flame retardants halogenated alkyl phosphate in rats. *Jap J Toxicol Environ Health* 34(2):102−114. 656593

Mobil Oil Corporation. (1981) A murine lymphoma mutagenesis assay, heterozygous at the thymidine kinase locus for the determination of the potential mutagenicity of Antiblaze 80 (unpublished). Environmental Affairs and Toxicology Department, Albright & Wilson Americas. Inc., New York, Report No. 2422-80. As cited in OECD (2000) and Albright and Wilson Americas (1989). 670280

Nakamura, A; Tateno, N; Kojima, S; et al. (1979) The mutagenicity of halogenated alkanols and their phosphoric acid esters for Salmonella typhimurium. *Mutat Res* 66(4):373−380. Available online at http://dx.doi.org/10.1016/0165-1218(79)90048-X. 625040

NICNAS (National Industrial Chemicals Notification and Assessment Scheme). (2001) Trisphosphates: Priority existing chemical assessment report. NICNAS, Sydney, Australia; Report No. 17. Available online at http://www.nicnas.gov.au/Publications/CAR/PEC/PEC17.asp. 656598

NIHS (National Institute of Health Science). (1994) Studies on the toxicity of insecticides and food additives in pregnant rats - foetal toxicity of tris-(chloropropyl) phosphate, with cover letter dated 10/12/94. National Institute of Health Sciences, Osaka, Report No. 86950000008. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0557521. 656604

NIOSH (National Institute for Occupational Safety and Health). (2011) NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare, Atlanta, GA. Available online at http://www.cdc.gov/niosh/npg/npgdcas.html. Accessed on 9/12/2011. 625692

NTP (National Toxicology Program). (2011a) 90 Days dosed-feed toxicity study of tris(2-chloroisopropyl)phosphate (TCPP) (CAS No. 13674-84-5) in B6C3F1 Mice. NTP Study Number C20712. Research Triangle Park, NC. 1325320

NTP (National Toxicology Program). (2011b) Study data from study number C20712: "90 Days dosed-feed toxicity study of tris(2-chloroisopropyl)phosphate (TCPP) (CAS No. 13674-84-5) in B6C3F1 Mice". Available online at http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?study_no=C20712&study_length=90%20Days. Accessed on 9/12/2011. 1325321

NTP (National Toxicology Program). (2011c) 12th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Available online at http://ntp-server.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15. Accessed on 9/12/2011. 737606

OSHA (Occupational Safety and Health Administration). (2006) Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. U.S. Department of Labor, Washington, DC; OSHA Standard 1915.1000. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286. Accessed on 9/12/2011. 625691

Sprague, GL; Sandvik, LL; Brookins-Hendricks, MJ; et al. (1981) Neurotoxicity of two organophosphorus ester flame retardants in hens. *J Toxicol Environ Health* 8(3):507−518. Available Online at http://dx.doi.org/10.1080/15287398109530087. 656590

Stauffer Chemical Company. (1978a) Mutagenicity evaluation of Fyrol PCF in the Ames Salmonella/microsome plate test. Stauffer Chemical Company, Westport, CT; Report No. T6361. As cited in OECD (2000). 656591

Stauffer Chemical Company. (1978b) Mutagenicity evaluation of Fyrol PCF in the mouse lymphoma forward mutation assay. Stauffer Chemical Company, Westport, CT, Report No. T6343A. As cited in OECD (2000). 656594

Stauffer Chemical Company. (1978c) Mutagenicity evaluation of Fyrol PCF in the in vitro transformation of BALB/3T3 cells assay. Stauffer Chemical Company, Westport, CT; Report No. T6357A. As cited in OECD (2000). 672972

Stauffer Chemical Company. (1978d) Evaluation of Fyrol PCF, Lot #8400-3-10 in the in vitro transformation of BALB/3T3 cells assay. Stauffer Chemical Company; Westport, CT, Report No. T-6359; Litton Project No. 20992. As cited in OECD (2000). 672973

Stauffer Chemical Company. (1978e) Evaluation of Fyrol PCF Lot 8400-3-10 in the unscheduled DNA synthesis in human WI-38 cells assay. Stauffer Chemical Company, Westport, CT; Report No. T6359; Litton Project No. 20991. As cited in OECD (2000). 656592

Stauffer Chemical Company (1978f) Mutagenicity evaluation of Fyrol PCF (Lot No. 4800-3-10) in the rat bone marrow cytogenetic analysis. Stauffer Chemical Company, Westport, CT; Report No. T-6539. As cited in OECD (2000). 672971

Stauffer Chemical Company. (1980a) Fyrol PCF: A two-week acute dietary range-finding study in male and female Charles River Sprague-Dawley derived rats. Stauffer Chemical Company, Westport, CT; Report No. T-10112. As cited in OECD (2000). 656596

Stauffer Chemical Company. (1980b) Fyrol PCF (Lot No. 4800-3-10) morphologic transformation of BALB/3T3 cells. Stauffer Chemical Company, Westport, CT; Report No. T-10182. As cited in OECD (2000). 672970

Stauffer Chemical Company. (1981) Fyrol PCF: 3-month dietary subchronic study in rats. Stauffer Chemical Company, Westport, CT; Report No. T-10118. As cited in OECD (2000). 1325323

Stauffer Chemical Company. (1984) Fyrol PCF metabolism/pharmacokinetic study in rats. stauffer chemical company, Westport, CT; Report No. T-10851. As cited in OECD (2000). 672969

OECD (Organisation for Economic Co-operation and Development). (2000) Tris(1-chloro-2-propyl)phosphate. Screening Information Data Set (SIDS). Geneva, Switzerland: UNEP Publications. Available online at http://www.chem.unep.ch/irptc/sids/oecdsids/13674845.pdf. 656600

U.S. EPA (Environmental Protection Agency). (1988) Recommendations for and documentation of biological values for use in risk assessment. Environmental Criteria and Assessment Office, Cincinnati, OH; EPA/600/6-87/008. Available online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855#Download. 064560

U.S. EPA (Environmental Protection Agency). (1994a) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC; EPA/600/R-94/904. Available online at http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt. 596444

U.S. EPA (Environmental Protection Agency). (1994b) Methods for derivation of inhalation reference concentrations (RfCs) and application of inhalation dosimetry. Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC; EPA/600/8-90/066F. Available online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993. 006488

U.S. EPA (Environmental Protection Agency). (2009) 2009 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA/822/R-09/011. Available online at http://deq.state.wy.us/wqd/groundwater/downloads/dwstandards2009%5B1%5D.pdf. Accessed on 9/12/2011. 086237

U.S. EPA (Environmental Protection Agency). (2011a) Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/. Accessed on 9/12/2011. 003752

U.S. EPA (Environmental Protection Agency). (2011b) Health effects assessment summary tables (HEAST). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. Available online at http://epa-heast.ornl.gov/. Accessed on 9/12/2011. 595422

Zeiger, E; Anderson, B; Haworth, S; et al. (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen* 19(Suppl 21):2−141. Available online at http://dx.doi.org/10.1002/em.2850190603. 095748