Toxicological Risks of Selected Flame-Retardant Chemicals

Subcommittee on Flame-Retardant Chemicals, Committee on Toxicology, Board on Environmental Studies and Toxicology, National Research Council

ISBN: 0-309-59232-1, 534 pages, 6 x 9, (2000)

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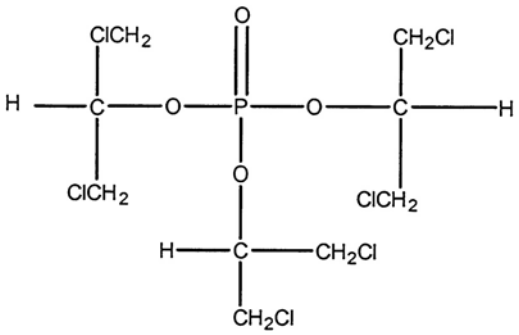
Tris (1,3-dichloropropyl-2) Phosphate

THIS chapter reviews the physical and chemical properties, toxicokinetics, toxicological, epidemiological, and exposure data on tris (1,3-dichloropropyl-2) phosphate, or TDCPP. The subcommittee used that information to characterize the health risk from exposure to TDCPP. The subcommittee also identified data gaps and recommended research relevant for determining the health risk from exposure to TDCPP.

PHYSICAL AND CHEMICAL PROPERTIES

TDCPP is a chlorophosphonate that is used as a fire retardant and plasticizer in various plastic foams, resins, and latexes in the U.S. and Europe (IPCS 1998). Chemical and physical properties of TDCPP are reported in Table 16–1. TDCPP is a viscous, colorless liquid; is not volatile; and is soluble in water and most organic solvents. It is manufactured from epichlorohydrin and phosphorus oxychloride and contains 49% chlorine and 7.2% phosphorus by weight (HSDB 1989). The commercial product consists mainly of 1,3-dichloro-2-propyl groups but can contain trace amounts of tris(2,3-dichloropropyl) phosphate (CAS 78–43–3). TDCPP has been mistakenly referred to as TCPP, which is tris(1-chloro-2-propyl) phosphate (CAS 13674–84–5).

TABLE 16–1 Chemical and Physical Properties of Tris(1,3-dichloropropyl-2) Phosphate

Properties	Value	Reference
Chemical formula	$C_9H_{15}Cl_6O_4P$	HSDB 1989; IPCS 1998
Structure		
CAS Registry #	13674–87–8	HSDB 1989; IPCS 1998
Synonyms	1,3-Dichloro-2-propanol phosphonate (3:1); Phosphoric acid tris (1,3-dichloro-2-propyl)ester; 2-Propanol, 1,3-dichloro-, phosphate (3:1); Tris(2-chloro-1-(chloromethyl)ethyl)phosphate; Tris(1-chloromethyl-2-chloroethyl) phosphate; Tris(1,3-dichloroisopropyl)phosphate; Tris(1,3-dichloro-2-propyl)-phosphate; chloroalkyl phosphate; TDCPP; TDCP; TCPP	IPCS 1998
Trade names	Fyrol FR2; PF 38; PF 38/3; Firemaster T33P; CRP; Apex Flame Proof Emulsion 197 or 212; Antiblaze 195; Amgard; Foforan Troj-(1,3-dwuchloroizopropylowy (Polish)	HSDB 1989; IPCS 1998
Molecular weight	430.88	HSDB 1989
Physical state	viscous liquid	IPCS 1998
Solubility	100 ppm or 7 mg/1 in H_2O (temp, not given) 100 mg/l in H_2O (30°C)	HSDB 1989; IPCS 1998
Vapor pressure	0.01 mm Hg at 30°C	IPCS 1998
Partition coefficient	log K_{ow}=3.76	HSDB 1989; IPCS 1998
Specific gravity	1.52 at 25 °C	IPCS 1998
Boiling point	236–237°C at 5 mm Hg	HSDB 1989, IPCS 1998
Flash point	252 °C (Cleveland open cup method)	IPCS 1998
Viscosity	1,800cP(25°C)	IPCS 1998
Conversion factors	1 ppm= 0.0567 mg/m^3 1 mg/m^3=17.62 ppm	IPCS 1998

OCCURRENCE AND USE

TDCPP was first synthesized by chemists of the Stauffer Chemical Company in the 1950s. It was introduced as a flame retardant commercially in 1962 and was later given the commercial trade name Fyrol® FR2 (Sanders 1978). It has been produced by other chemical companies under the trade names Emulsion 212, PF 38, and PF38/3.

Annual worldwide demand for TDCPP in 1997 was estimated at 8,000 tons and was growing (IPCS 1998). Current volume of use in the U.S. was not located, but TDCPP appears in the US Environmental Protection Agency's (EPA) 1990 list of high production volume chemicals (chemicals that are manufactured or imported into the U.S. at greater than 1 million lb/yr).

TDCPP is added as a flame retardant and plasticizer to polyurethane foam (both rigid and flexible), other plastics and resins, and latexes for textile backcoating and binding of nonwoven fabrics (IPCS 1998). It is also applied as a flame retardant in polyisocyanurate foams, automotive seating, and styrenebutadiene rubber (HSDB 1989). A 1997 survey of producers of flame retardants marketed to the textile industry found that TDCPP was used as a flame retardant in automobile and truck upholstery, draperies, and wall coverings in the U.S. and in commercial and residential furniture and “other transportation” upholstery outside the U.S. (Fire Retardant Chemicals Association 1998).

TDCPP was used as a flame retardant in childrens, and infants sleepware until May 1977, when it was withdrawn from sales to the apparel market after published reports that it was mutagenic in bacteria (Sanders 1978).

TOXICOKINETICS

Absorption

Dermal

Experimental animal data suggest that TDCPP is absorbed extensively from the skin, but the rate or extent of absorption has not been measured. Nomeir et al. (1981) reported that TDCPP was readily absorbed through the skin of rats treated topically with 60 µL of a methanol-TDCPP solution on a 4-cm^2 area at a concentration of 2.0 µmol/kg. Each animal was treated with 60 µL/kg solution. The 60 µL was applied to a 4-cm^2 area of skin. Ulsamer et al. (1980) reported that the dermal absorption of TDCPP in rats and rabbits was about twice that of tris(2,3-dibromopropyl) phosphate (Tris). The dermal penetration of Tris was reported to be about 3.0–15.0% in rabbits (Ulsamer et al. 1980).

Inhalation

No studies were identified that investigated the absorption of TDCPP by the dermal, inhalation, or oral routes in humans or laboratory animals.

Oral

TDCPP is readily absorbed through the GI tract in rodents. Matthews and Anderson (1979) reported that about 90% of an unstated oral dose of TDCPP was absorbed through the gut wall in rats. Nomeir et al. (1981) also found that about 90% of TDCPP given orally at 0.2, 2.0, and 20.0 μmol/kg was absorbed from the rat gut within 24 hr. Similar results were reported by Minegishi et al. (1988) for rats given TDCPP at 50 μmol/kg by gavage.

Distribution

Dermal

Distribution of TDCPP in rats after topical application of TDCPP at 2.0 μmol/kg was studied by Nomeir et al. (1981). Most of the dermal dose was found in the liver, lungs, skin, and kidneys at 4 hr after application. Smaller amounts were found in adipose tissue, muscle, and blood.

Inhalation

No studies were identified that investigated the distribution of TDCPP following inhalation exposure in humans or laboratory animals.

Oral

TDCPP is distributed primarily to the lungs, liver, and kidneys within 24 hr of oral administration in rats (Minegishi et al. 1988, Nomeir et al. 1981). TDCPP is also distributed to a lesser extent to the heart, adipose tissue, skin, brain, spleen, and gonads after oral administration in rats.

Other Routes of Exposure

Morales and Mathews (1980) reported that [^{14}C]-TDCPP readily bound with the DNA present in the liver of male CD-1 mice. Mice were given a single intravenous dose of TDCPP at 94.4 µmol/kg and sacrificed 6 hr later. TDCPP in liver DNA was estimated at 8.3 ± 2.3 pmol/mg. Traces of radioactivity were detected in kidney DNA and none in muscle; much larger amounts were detected in protein and low-molecular-weight RNA isolated from liver and kidney.

Metabolism

No studies were identified that have investigated the metabolism of TDCPP in humans or laboratory animals following dermal, inhalation, or oral exposure.

The major urinary metabolite of TDCPP formed in rats is bis(1,3-dichloro-2-propyl) phosphate 24 hr after following intraperitoneal injection (Lynn et al. 1981). Of radiolabeled TDCPP, 54% was excreted in the urine within 5 d and 62% of the urinary label was bis(1,3-dichloro-2-propyl) phosphate. Two other metabolites isolated were 1,3-dichloro-2-propyl phosphate and 1,3-dichloro-2-propanol.

TDCPP was rapidly metabolized in vitro by an NADPH-dependent microsomal mixed-function oxidase system and glutathione S-transferases from rat liver to 1,3-dichloro-2-propanol, 3-chloro-1, 2-propanediol, bis (1,3-dichloro-2-propyl) phosphate, and one unidentified metabolite that was thought to be a glutathione conjugate (Nomeir et al. 1981).

Excretion

No studies were identified that have investigated the excretion of TDCPP in humans or laboratory animals following dermal or inhalation exposure.

Minegishi et al. (1988) reported that 43% of a single oral dose of TDCPP at 50 µmol/kg in rats was excreted in the urine within a week of exposure; 39% and 16% were excreted in the feces and air, respectively. About 2.5% of the administered dose remained in the carcass. Those studies also demonstrated that TDCPP is extensively excreted (40%) in the bile; this increases the retention time of TDCPP because of enterohepatic recirculation.

Nomeir et al. (1981) found that intravenous TDCPP at 2.0 µmol/kg in rats was eliminated primarily in the bile, feces, and urine; some small amounts were eliminated as CO_2. About 80% of the intravenous dose was eliminated within 24 hr, but traces of radioactivity were found in most tissues 10 d after exposure.

HAZARD IDENTIFICATION[1]

Dermal Exposure

Irritation

Citing industrial reports and an unpublished chronic dermal-toxicity study of TDCPP in rabbits, Ulsamer et al. (1980) stated that TDCPP had been shown not to be a primary irritant. Piotrowski et al. (1976), cited in the entry for TDCPP in the Hazardous Substances Data Bank (HSDB) reported that TDCPP did not produce irritation in rabbit skin or sensitization reactions in guinea pig skin; however, no details on the amounts of TDCPP applied were available to the subcommittee.

The International Programme on Chemical Safety (IPCS)(1998) reports that TDCPP irritated rabbit skin in a 1989 industry-sponsored study. The irritating properties of TDCPP were evaluated in three New Zealand white rabbits via a patch test at an unspecified dose. Well-defined erythema was recorded in two animals an hour after patch removal; slight erythema was observed in the third animal at the contact site. All exposed sites had returned to normal 48 hr after exposure.

Sensitization

No studies were identified that investigated the sensitizing potential of TDCPP following repeated dermal application in humans or laboratory animals.

Systemic Effects

Dermal LD_{50} s of TDCPP in rats and rabbits are consistently above 2,000 mg/kg (IPCS 1998). Ulsamer et al. (1980) reported that one unpublished study had found that the LD_{50} in male albino rabbits was greater than 23.9 g/kg when TDCPP was applied with an occlusive bandage. At that dose, rabbits were irritable and had diarrhea, miosis, and increased muscle tonus as evidenced by trembling; these effects persisted during most of the unstated observation period. Ulsamer et al. also reported that no deaths or toxic signs were observed 14 d after exposure in albino rabbits treated topically with TDCPP of 4.64 g/kg for 24 hr.

[1]In this section, the subcommittee reviewed toxicity data on tris(1,3-dichloropropyl-2) phosphate, including the toxicity assessment prepared by the U.S. Consumer Product Safety Commission (Ferrante 1999).

Ulsamer et al. (1980) summarized the results of an unpublished chronic dermal-toxicity study of TDCPP in rabbits. Rabbits were exposed to TDCPP or TRIS at 1.45 g/kg for 90 d (frequency of dermal application not stated). Kidney weights were significantly increased in animals exposed to either compound. Histopathological analysis showed that TDCPP did not produce any effects in any tissues (examined tissue not stated).

Immunological Effects

The effects of subcutaneous injection of TDCPP on immune functions and host susceptibility to infectious agents were investigated in groups of seven to 10 adult B6C3F$_1$ mice given TDCPP intravenously at 0, 0.25, 2.5, or 25 kg/d for 4 d (Luster et al. 1981). There were no clinical signs of toxicity in the treated mice, and no significant effects on body weight, organ weight, or histopathological status were detected. Immune measures evaluated in this study were bone marrow cellularity and colony formation, lymphoproliferative responses to mitogens, delayed hypersensitivity, and serum IgG, IgM, and IgA concentrations. TDCPP treatment induced minimal changes in immune functions and host susceptibility. The 25 mg/kg-d mice had lower proliferative responses to mitogens and higher tumor rates than nonexposed mice after tumor-cell implantation. No changes latent period for tumorigenicity were detected in the high-dose animals compared with controls.

Other Effects

No toxicity studies were found that investigated the toxic effects of topically-applied TDCPP on neurological, reproductive or developmental parameters in humans or laboratory animals. No studies were identified that investigated the carcinogenicity of TDCPP in humans or laboratory animals following dermal exposure.

Inhalation Exposure

Systemic Effects

The subcommittee located only one study that investigated the inhalation toxicity of TDCPP. IPCS (1998) cites a single industry-sponsored study that found that the LC_{50} of TDCPP was greater than 5,220 mg/m^3 in male and female Sprague-Dawley rats. There were no subchronic or chronic studies.

IPCS (1998) summarizes the results of a 1981 occupational-health survey by

Stauffer Chemical Company of 124 workers employed at a TDCPP-manufacturing plant in the U.S. The clinical and general health of 93 workers classified as having potential exposure to TDCPP was compared with that of 31 workers exposed to TDCPP and matched for age, alcohol consumption, and smoking. The investigation found no significant increase of morbidity in exposed workers compared with controls. Chest x-rays of the two groups were comparable. Abnormal electrocardiograms were twice as common among the exposed workers. No significance differences were seen in any clinical-chemistry measures investigated (measures not stated by IPCS). The prevalence of "minor respiratory disease" was slightly, but apparently not significantly, increased in exposed workers. Air samples taken in the plant within various area or job classifications all contained TDCPP at less than 0.4 $\mu g/m^3$.

Cancer

No studies were found that investigated the carcinogenicity of TDCPP by the inhalation route in humans or laboratory animals.

A 1981 mortality study at a Stauffer Chemical Company plant that manufactured TDCPP found an increased incidence of lung-cancer deaths in a cohort of 289 workers employed at the plant for at least 3 mo from 1956 to 1977 as compared to the incidence of lung cancer among the U.S. general population (comparison years not indicated). Three lung-cancer deaths occurred over this period for a standardized mortality ratio of 399. However, one of the three workers was identified as nonexposed, and another was employed for only 2 yr. All three were reported to be heavy smokers. No TDCPP was detected in air samples from various job or exposure areas of the plant (maximal detection limit, 0.13 mg/m^3).

Other Effects

No toxicity studies were identified that investigated the effects of TDCPP on the immune system, nervous system, the reproductive system, development, or behavior in humans or laboratory animals following inhalation exposure.

Oral Exposure

Systemic Effects

TDCPP does not appear to be a potent acute toxicant on the basis of reported oral LD_{50}s in rodents (see Table 16–2). Reported oral LD_{50}s for TDCPP are

1.85–4.5 g/kg in rats, 2.25–2.67 g/kg in mice, and 6.8 g/kg in rabbits. Typical clinical signs of toxicity in rats given high doses of TDCPP are hypokinesia, rpiloerection, soiled coats, ataxia, irritability, hyperactivity, convulsions, tetanus, rhinorrhea, salivation, and congestion of heart, lungs and liver (Celanese Corp. 1960, as cited in Ulsamer et al. 1980; Osterberg and Bierbower 1978, as cited in Ulsamer et al. 1980; Kamata et al. 1989). One study reported fatty degeneration and renal necrosis (Piotrowski et al. 1976, as cited in HSDB 1989); the remaining studies indicated no remarkable histopathological effects

TABLE 16–2 LD50 and LC50 Data for Tris(1,3-dichloropropyl-2) Phosphate

Route	Species	LD_{50}/LC_{50}	Study
Oral	Rat	3.16 g/kg	Stauffer Chemical Co. 1981
		2.83 g/kg	Celanese Corp. 1960, as cited in Ulsamer et al. 1980
		2.36 g/kg	Osterberg and Bierbower 1978, as cited in Ulsamer et al. 1980
		1.85 g/kg (frationated: small doses over 120 hr) 4.5 g/kg (frationated: large doses over 48 hr)	Piotrowski et al. 1976, as cited in HSDB 1989
	Mouse	4.99 mL/kg	Stauffer Chemical Company 1977–78, as cited in Ulsamer et al. 1980
		2.67 g/kg (males) 2.25 g/kg (females)	Kamata et al. 1989
	Rabbit	6.8 g/kg	Azko Nobel 1998, as cited in CPSC 1999
Dermal	Rabbit	>23.9 g/kg	Celanese Corp. 1960, as cited in Ulsamer et al. 1980
		>4.64 g/kg	Stauffer Chemical Company 1977–78, as cited in Ulsamer et al. 1980
		>15 mL/kg	Azko Nobel 1998, as cited in CPSC 1999
Inhalation	Rat	>9.8 mg/L	Azko Nobel 1998, as cited in CPSC 1999

(Celanese Corp. 1960, as cited in Ulsamer et al. 1980; Osterberg and Bierbower 1978, as cited in Ulsamer et al. 1980).

Increases in relative liver and kidney weights and in mortality, were observed in mice fed TDCPP for 3 mo in their diet (Kamata et al. 1989). Male mice were given TDCPP at 0, 13, 47, 171, 576, or 1,792 mg/kg-d in their diet, and females were given TDCPP at 0, 15, 62, 214, 598, or 1,973 mg/kg-d. Males and females in the high-dose groups (1,792 and 1,973 mg/kg-d) all died within a month; they were emaciated and had rough hair coats and tremor. Liver weights in males after 3 mo at 171 and 576 mg/kg-d were increases by 32% and 51%, respectively. Liver weight in females after 3 mo at 62, 214, and 598 mg/kg-d were statistically significantly increased by 16%, 29%, and 51%, respectively. Significant increases in kidney weights were observed—by an average of 39%—in male mice fed 576 mg/kg-d and significant increases in relative kidney weight of 34 and 40% were observed in female mice fed 214 and 598 mg/kg-d, respectively. Histopathological examination showed slight necrosis of liver tissue in two female mice fed 598 mg/kg-d for 3 mo. No other statistically significant findings were reported. Decreased hemoglobin concentration was observed in males given 576 mg/kg-d and females given 598 mg/kg-d. Increases in serum alkaline phosphatase and serum alanine aminotransferase were observed with increasing exposure but were not statistically significantly elevated after 3 mo. The no-observed-adverse-effect level (NOAEL) for the increase in liver weight was 47 mg/kg-d in males and 15 mg/kg-d for females. The lowest observed-adverse-effect level (LOAEL) for significantly increased liver weight was 171 mg/kg-d in males and 62 mg/kg-d for females (IPCS 1998).

Statistically significant increases in mortality; in liver, kidney, and thyroid weights; and in abnormal histopathological findings were observed in Sprague-Dawley rats fed TDCPP in their diet for 12 and 24 mo in an unpublished study conducted by Bio/dynamics for Stauffer Chemical Company (Bio/dynamics 1981). Male and female Sprague-Dawley rats (60/sex/group) were given TDCPP in the diet at 0, 5, 20, and 80 mg/kg-d. Ten animals/sex/dose group were sacrificed after 12 mo, and the remaining animals were sacrificed at 24 mo. Mortality among the high-dose males was significantly increased as compared with controls at 17 mo. Mortality was not significantly increased among males or females at 12 mo, and mortality was not significantly higher among females in the 80 mg/kg-d dose group or in males or females of the 5 or 20 mg/kg-d dose groups at 24 mo. Chronic exposure to TDCPP did not result in significant clinical signs representative of toxicity in any of the dose groups at any time during the study. Body weights were significantly decreased in high-dose male and females beginning at 7 wk. Mean organ weights and organ: body weight ratios were increased for liver, kidneys and thyroid at 12 and 24 mo in males and females given 80 mg/kg-d (see Table 16–3). At 24 mo, the incidence

TABLE 16–3 Changes in Organ Weights and Organ/Body Weight Ratios in Sprague-Dawley Rats Fed Tris(1,3-dichloropropyl-2) Phosphate (mg-kg-d)

	Males				Females			
Tissue	0	5	20	80	0	5	20	80
12 Month Mean Values								
LIVER								
Organ weight (mg)	13.86	14.98	15.50	17.52[a]	8.17	8.73	8.70	10.10[a]
Organ/body weight ratio	2.39	2.49	2.89	3.56[a]	2.60	2.56	2.72	3.25[a]
KIDNEY								
Organ weight (mg)	3.19	3.57	3.74	4.70	2.03	2.18	2.27	2.84[a]
Organ/body weight ratio	0.56	0.60	0.70[a]	0.95[a]	0.65	0.64	0.73	0.92[a]
THYROID								
Organ weight (mg)	0.028	0.030	0.032	0.035	0.020	0.024	0.025	0.024
Organ/body weight ratio	0.0049	0.0050	0.0060	0.0072[a]	0.0062	0.0072	0.0078[a]	0.0077[a]
24-Month Mean Values								
LIVER								
Organ weight (mg)	14.43	14.74	16.33[a]	16.77[a]	10.55	11.27	11.39	12.20
Organ/body weight ratio	2.40	2.58	3.27[a]	4.00[a]	2.75	2.80	3.29[a]	4.62[a]
KIDNEY								
Organ weight (mg)	3.74	3.94	5.49[a]	5.75[a]	2.64	2.96	3.42[a]	4.34[a]
Organ/body weight ratio	0.63	0.67	1.14[a]	1.34[a]	0.71	0.74	0.98[a]	1.40[a]
THYROID								
Organ weight (mg)	0.040	0.038	0.039	0.043	0.029	0.030	0.030	0.034[a]
Organ/body weight ratio	0.0066	0.0068	0.0079[a]	0.0102[a]	0.0077	0.0076	0.0086	0.0110[a]

[a]$p<0.05$; chi square analysis.
Source: Adapted from Bio/dynamics 1981.

of altered liver foci was significantly increased ($p < 0.05$) in females given 80 mg/kg-d, and the incidence of convoluted tubule hyperplasia was significantly increased in males given 20 and 80 mg/kg-d and females given 80 mg/kg-d (Table 16–4). An increased incidence of bone marrow erythroid-myeloid hyperplasia was observed in males and females given 80 mg/kg-d, but no bone marrow samples were taken from males or females in the lower-dose groups.

Ulsamer et al. (1980) reported increased mortality in rats given TDCPP by gavage at 25.0 or 250.0 mg/kg-d for 90 d. Numbers of deaths were notreported. The authors noted that absolute and relative liver and kidney weights were significantly increased in both dose groups. Histopathological evaluation showed "no remarkable differences in any tissues."

Immunological Effects

No oral-toxicity studies of TDCPP were located that investigated effects on the immune system.

Neurological Effects

Exposure to TDCPP at high concentrations produces various clinical symptoms, such as convulsions and hyperactivity, that could be the result of direct interaction of TDCPP with nervous tissue (see Systemic Effects of Oral Exposure section under Hazard Identification).

Ulsamer et al. (1980) fed chickens TDCPP at 0.6, 1.2, 2.4, or 4.8 g/kg-d for 5 d. Chickens fed 1.2 mg/kg-d or more exhibited leg and wing weakness (flaccid paralysis); all the chickens given 4.8 mg/kg-d died. It was determined that TDCPP had about 5% of the paralyzed activity of tri-o-cresyl phosphate (TOCP), a known neurotoxicant in chickens.

No neurotoxicity was observed in 12-mo old white leghorn hens 21 d after being fed TDCPP at 420 mg kg-d for 5 d (Bullock and Kamienski 1972, as cited in IPCS 1998). TOCP fed to control hens induced inability to walk, hypertension, ataxia, and prostration.

Reproductive and Developmental Effects

Wilczynski et al. (1983) investigated the effects of TDCPP following oral exposure on reproductive measures in male rabbits. No adverse effects on various reproductive measures were observed in male rabbits treated with

TDCPP by gavage at 0, 2 20 or 200 mg/kg-d for 12 wk. Reproductive measures evaluated were mating behavior, fertility, and sperm quantity and quality.

TABLE 16–4 Histopathological Observations in Sprague-Dawley Rats Fed Tris(1,3-dichloropropyl-2) Phosphate (mg/kg-d)

	Males				Females			
Tissue	0	5	20	80	0	5	20	80
LIVER								
Altered foci	22/60	20/60	16/60	31/60	16/60	23/60	19/55	36/60[a]
KIDNEY								
Convoluted tubule hyperplasia	2/60	10/60	29/60[a]	24/59[a]	0/60	1/60	3/57	22/60[a]
Nephropathy	39/60	26/60	36/60	39/59	12/60	13/60	11/57	25/60
SPLEEN								
Erythroid/myeloid metaplasia	13/60	3/6	4/6	17/58	13/60	5/6	3/4	33/60[a]
PARATHYROID								
Hyperplasia	1/29	1/1	0/2	12/38[a]	6/29	—	—	9/28
TESTES								
Oligospermia	35/57	31/60	45/60	51/56	NA	NA	NA	NA
Eosinophic material/lumen	2/57	4/60	12/60[a]	11/56	NA	NA	NA	NA
Sperm stasis	5/57	5/60	11/60	14/56	NA	NA	NA	NA
Periateritis nodosa	5/57	10/60	19/60[a]	16/56[a]	NA	NA	NA	NA
EPIDIDYMES								
Oligospermia	11/55	9/33	7/14	36/55[a]	NA	NA	NA	NA
Degenerated seminal product	8/55	7/33	3/14	22/55[a]	NA	NA	NA	NA
SEMINAL VESICLE								
Decreased secretory product	1/56	11/13[a]	17/20[a]	23/52[a]	NA	NA	NA	NA
Atrophy	0/56	4/13[a]	6/20[a]	10/52[a]	NA	NA	NA	NA

NA, not applicable.
[a]$p < 0.05$; chi square analysis.
Source: Adapted from Bio/dynamics 1981.

Three studies were located that investigated the developmental and maternal toxicity of oral TDCPP in rats: Stauffer Chemical Company 1977–78; Tanaka er al. 1981; and Kawashima et al. 1983. Doses given to pregnant rats were as

follows: Stauffer Chemical Company (1977–78) 0, 25, 100, or 400 mg/kg-d on d 6–15 of gestation; Tanaka et al. (1981) 0, 25, 50, 100, 200, or 400 mg/kg-d on d 7–15 of gestation; andKawashimaetal. (1983) 0, 25, 50, 200, or 400 mg/kg-d on d 7–15 of gestation. None of the studies found that TDCPP caused developmental abnormalities in surviving fetuses despite an increased incidence of fetal and maternal toxicity in the high-dose groups. Fetal toxicity was characterized by increased incidence of fetal death, decreased fetal weight, decreased fetal length, or increased incidence of resorption. Maternal toxicity observed at 100 mg/kg-d or greater was characterized by reduced body weight and reduced food consumption compared with negative controls (Stauffer Chemical Company 1977–78; Kawashima et al. 1983). Tanaka et al. (1981) observed significant increases in kidney weights in pregnant rats given 200 or 400 mg/kg-d; rats given 400 mg/kg-d also had a higher incidence of reduced body-weight gain and higher incidences of piloerection, salivation, and hematuria. Tanaka et al. (1981) concluded that the no-observed-adverse-effects level (NOAEL) for developmental effects in their study was 400 mg/kg-d although it was not determined whether the observed fetal effects were related to maternal toxicity. It was concluded that the NOAEL and lowest observed-adverse effects level (LOAEL) for maternal toxicity in this study were 100 and 200 mg/kg-d, respectively.

Cancer

An increase in the incidence of various tumors was observed in male and female Sprague-Dawley rats chronically exposed to TDCPP for 104 wk (Bio/dynamics 1981). The tumor incidence for this study at 104 wk is summarized in Table 16–5. Statistically significant increases in the incidence of liver adenomas and of liver adenomas and carcinomas combined were observed in males and females given 80 mg/kg-d. Although the increase in the incidence of liver carcinomas was not statistically significant at 104 wk, it is assumed that some adenomas would progress to carcinomas if the in-life phase of the study was extended. A statistically significant increase in the incidence of renal cortical tumors was also observed in males and females fed 20 and 80 mg/kg-d. The incidence of testicular interstitial-cell tumors was significantly increased in males fed 20 and 80 mg/kg-d. The incidence of adrenal cortical adenomas was increased significantly in female mice fed 80 mg/kg-d.

Genotoxicity

A number of genotoxicity studies on TDCPP have been completed. They are summarized in Table 16–6. TDCPP was uniformly positive for mutagenicity in

the Ames assay in the presence of rat S9 liver fraction. It was weakly clastogenic in mouse lymphoma cells in the presence or absence of mouse S9 liver fraction (Brusick et al. 1980). It was also weakly positive in the UDS assay with rat hepatocytes (Soderlund et al. 1985). In vivo studies have failed to demonstrate consistently that TDCPP is a genotoxicant in mammalian test systems. The TDCPP metabolite 1,3-dichloro-2-propanone has been shown to be a direct-acting mutagen in the Ames assay (Gold et al. 1978); The metabolite 1,3-dichloro-2-propanol was found to be weakly mutagenic in the same study. Similar results have been reported by Lynn et al. (1981). Overall, the data indicate that TDCPP might be mutagenic after metabolic activation.

Table 16–5 Tumor Incidence Among Sprague-Dawley Rats Fed for Tris(1,3-dichloropropyl-2) Phosphate 104 wk (mg/kg-d)

	Males				Females			
Tissue	0	5	20	80	0	5	20	80
LIVER								
Adenoma	2/60	7/60	1/60	16/60[a]	1/60	1/60	4/55	9/60[a]
Carcinoma	1/60	2/60	3/60	7/60	0/60	2/60	2/55	4/60
Adenoma and carcinoma combined	3/60	9/60	4/60	23/60[a]	1/60	3/60	6/55	13/60[a]
KIDNEY								
Cortical tumor	1/60	3/60	9/60[a]	32/59[a]	0/60	1/60	8/57[a]	29/60[a]
TESTES								
Interstitial cell tumor	7/57	8/60	26/60[a]	39/56[a]	NA	NA	NA	NA
ADRENAL								
Cortical adenoma	5/59	3/14	5/16	5/57	13/59	5/27	2/33	20/59[a]

NA, not applicable.
*a*p<0.05 as compared with controls.
Source: Adapted from Bio/dynamics 1981.

QUANTITATIVE TOXICITY ASSESSMENT

Noncancer

Dermal Assessment

The dermal-toxicity data available on TDCPP are not adequate for developing a dermal RfD. One unpublished subchronic dermal-toxicity study in rabbits

TABLE 16–6 Summary of Genotoxicity Studies of Tris(1,3-dichloropropyl-2) Phosphate

Assay	Results (−S9)	Results (+S9)	Comments	Study
IN VITRO STUDIES				
Gene Mutation: *S. typhimurium*				
Tris(1,3-dichloropropyl-2) Phosphate				
TA 100	NT	9	Mouse S9—phenobarbital induced	Gold et al. 1978
TA 100	NT	–	Mouse and Rat S9—PCB induced	Brusick et al. 1980
TA 100	NT	–	Rat S9—phenobarbital induced	Brusick et al. 1980
TA 100	NT	+	Mouse S9—phenobarbital induced	Brusick et al. 1980
TA 100	NT	–	Human S9	Brusick et al. 1980
TA 100	–	+	Rat S9—PCB induced	Nakamura et al. 1979
TA 1535	±	+	Rat S9—PCB induced	Nakamura et al. 1979
TA 100	NT	+	Rat S9—phenobarbital induced	Soderlund et al. 1985
TA 100	NT	–	Metabolic activation by co-culture with hepatocyte monolayer from phenobarbital-treated rats	Soderlund et al. 1985
TA 100	NT	±	Rat S9—PCB induced or mouse S9 - phenobarbital induced. Positive response only at high cytotoxicity (<3% survival). Unclear for which S9 system data were reported.	Majeska and Matheson 1983
TA 100	–	±	Mouse S9—phenobarbital induced	Lynn et al. 1981
TA 1538	–	–	Rat S9—PCB induced	Prival et al. 1977
Tris (1,3-dichloropropyl-2) Phosphate Metabolites				
TA 100	NT	0	Mouse S9—phenobarbital induced	Gold et al. 1978
	++			Lynn et al. 1981
TA 100	++	NT		Gold et al. 1978

Assay	Results (−S9)	Results (+S9)	Comments	Study
TA100, TA1535, TA98, TA1537	++		Urine from mice dosed by gavage for 4 d with tris(1,3-dichloroisopropyl) phosphate up to 0.5 mL/kg	Brusick et al. 1980
Gene Mutation: *E. coli*				
	–	–	Activation system not described	Ulsamer et al. 1980
Mammalian Systems				
L5178Y mouse lymphoma	–	–	Mouse S9—phenobarbital induced	Brusick et al. 1980
V79 Chinese Hamster Lung	NT	–	Rat S9—phenobarbital induced; tested to only 19% cytotoxicity, 0.02 mM high dose	Soderlund et al. 1985
DNA Damage Assays				
Unscheduled DNA synthesis rat hepatocytes	±	–	Hepatocytes derived from untreated or phenobarbital-treated rats	Soderlund et al. 1985
Sister chromatid exchange in	±	±	Mouse S9—PCB induced	Brusick et al. 1980
L5178Y mouse lymphoma cells	±	±	Mouse S9—phenobarbital induced	Brusick et al. 1980
Chromosome Aberration				
Mouse lymphoma cells	±	+	Mouse S9—PCB induced	Brusick et al. 1980
	±	+	Mouse S9—phenobarbital induced	Brusick et al. 1980
Morphological Transformtation				
Balb 3T3 cells	–	NT		Brusick et al. 1980
Syrian hamster embryo cells	+	NT		Soderlund et al. 1985
IN VIVO STUDIES				
Sex-linked recessive lethal	–		In *Drosophila*	Brusick et al. 1980.
Chromosome Aberration				
Mouse bone marrow	–		Mice exposed by gavage to 0.05, 0.17 or 0.5 mL/kg for 1 or 5 d	Brusick et al. 1980.
Chick embryo	–		No information provided	Bloom 1982 (cited by CPSC 1999)

−, negative; ±, weakly positive; +, positive; ++, strongly positive; NT, not tested (or results not reported in the CPSC (1999) summary.

is summarized in the review article by Ulsamer et al. (1980), but data necessary for deriving a dermal RfD based on this study are not reported. The study found an increase in kidney weights in treated rabbits—a response also reported in rodents orally exposed to TDCPP. Short-term dermal assays indicate that TDCPP causes minimal or no irritation to the skin and is not an effective sensitizer.

In the absence of a dermal RfD, the subcommittee believes it is appropriate to use the oral RfD for TDCPP of 0.005 mg/kg-d as the best estimate of the internal dose from dermal exposure.

Inhalation RfC

EPA has not developed an inhalation reference concentration (RfC) for TDCPP. The subcommittee found no adequate human or animal studies that could be used for deriving an inhalation RfC for TDCPP. A series of occupational-health investigations are available for a cohort of workers employed in a plant that manufactured TDCPP (Stauffer Chemical Company 1983a, 1983b, both as cited in IPCS 1998). However, air sampling failed to detect measurable amounts of TDCPP in various job or exposure areas frequented by the cohort in these investigations. Therefore, there are insufficient inhalation data to derive an inhalation RfC for TDCPP.

In the absence of relevant inhalation exposure data, the subcommittee chose to estimate inhalation RfCs from oral RfDs The subcommittee, however, recognizes that it is not an ideal approach and also recognizes that the estimated RfC levels might be considerably different than actual levels (if inhalation data were available). Extrapolating from one route of exposure (oral) to another (inhalation) requires specific knowledge about the uptake kinetics into the body by each exposure route, including potential binding to cellular sites. The subcommittee believes that its extrapolation of oral RfDs to inhalation RfCs is highly conservative; it assumes that all of the inhaled compound is deposited in the respiratory tract and completely absorbed into the blood. The NRC committee on Toxicology (NRC 1985) has used this approach when inhalation exposure data were insufficient to derive inhalation exposure levels. The subcommittee believes that such an approach is justified for conservatively estimating the toxicological risk from exposure to FRs. These RfCs should be used as interim or provisional levels until relevant data becomes available for the derivation of inhalation RfCs.

In order to calculate a hazard index for the inhalation route, a provisional inhalation RfC of 0.018 mg/m^3 was derived using the oral RfD for TDCPP and Equation 7 in Chapter 3.

Oral RfD

EPA has not developed an oral reference dose (RfD) for TDCPP. The oraltoxicity database relevant for developing an oral RfD for TDCPP consists of one subchronic study in mice (Kamata et al. 1989), one unpublished chronic study in rats (Bio/dynamics 1981), three developmental studies in rats (Stauffer Chemical Company 1977–78; Tanaka et al. 1981; Kewashima et al. 1983) and one male reproductive study in rabbits (Wilczynski et al. 1983). The subcommittee identified the chronic study by Bio/dynamics (1981) as the key study for deriving an oral RfD for TDCPP because the exposure period is of sufficient length (24 mo) and toxic effects occurred at dose levels in the rat that are lower than NOAELs reported for various effects in the TDCPP toxicity database.

There was statistically significant atrophy and decreased secretory product of the seminal vesicles in male rats fed diets containing 5 mg TDCPP/kg-d or greater. Animals were not tested at dose levels lower than 5 mg TDCPP/kg-d, therefore the subcommittee considered this dose level to be the LOAEL for testicular and seminal vesicle effects in this study.

Calculation of a benchmark dose for testicular effects was not possible, because of a lack of complete dose-response data on seminal vesical atrophy. This condition was investigated in all control and all high-dose males but not in males in the low- and medium-dose groups.

Using testicular and seminal vesicle effects as the critical effect and the LOAEL for these effects of 5 mg/kg-d, the oral RfD was then derived by applying a composite uncertainty factor (UF) of 1,000 yielding an oral RfD of 0.005 mg/kg-d (Table 16–7). An uncertainty factor (UF) for extrapolation to humans (UF_A) of 10 was applied to the NOAEL because there are no data for comparing the toxicokinetic and dynamic characteristics of TDCPP in rodents and humans. A UF of 3 was applied for intraspecies variability (UF_H) since developmental toxicity data does not indicate that immature animals are more sensitive to TDCPP than adults. A UF of 10 (UF_L) was applied because an LOAEL for organ toxicity was used to derive the oral RfD. An uncertainty factor of 3 (UF_D) was also applied because of the limited database for the toxicity of TDCPP.

The subcommittee has moderate confidence that the Bio/dynamics (1981) study identified the most critical toxic effects for TDCPP. Although the available data do not state that the study was conducted according to GLP procedures, Bio/dynamics (1981) appears to have been a well conducted study. However, this study is not peer-reviewed and does not establish a NOAEL for testicular effects related to TDCPP exposure.

The subcommittee has moderate confidence that the derived oral RfD will protect against noncancer toxic effects in most persons. That is based on its moderate confidence in the completeness of the toxicity database on TDCPP,

its moderate confidence in the sensitivity of the Bio/dynamics (1981) bioassay to detect critical toxic effects, and its inherently conservative approach to deriving the oral RfD. The subcommittee notes the presence of some uncertainty in the threshold dose associated with testicular and seminal vesicle effects after lifetime exposure in rodents.

TABLE 16–7 Oral Reference Dose for Tris(1,3-dichloropropyl-2) Phosphate

RfD (mg/kg-d)	Critical effect	Species	Effect level (mg/kg-d)	Uncertainty factors	Reference
0.005	Testicular atrophy and decreased seminal vesicle secretory product	Male rats	LOAEL: 5.0	UF_A: 10 UF_H:3 UF_L: 10 UF_D: 3 Total: 1,000	Bio/dynamics 1981

LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; RfD, reference dose; UF_A, extrapolation from animals to humans; UF_H, intraspecies variability; UF_L, NOAEL not determined for critical effect; UF_D, inadequate or deficient toxicity database

Cancer

The subcommittee is not aware of any scientific organizations or authoritative bodies that have evaluated the weight of evidence of the carcinogenicity of TDCPP. EPA has not developed a cancer assessment for TDCPP, and it has not been evaluated by the International Agency for Research on Cancer (IARC) or the National Toxicity Program (NTP).

Dermal

No studies were identified that investigated the carcinogenicity of TDCPP in humans or laboratory animals following dermal exposure.

Inhalation

No inhalation carcinogenicity data are available for TDCPP and an inhalation unit risk has not been derived. One epidemiological assessment was found of the potential carcinogenicity of TDCPP in workers with possible inhalation exposure to this compound (Stauffer Chemical 1983a, 1983b, both as cited in

IPCS 1998). Air samples failed to detect TDCPP in any of the potential job or exposure areas in the manufacturing plant investigated. Therefore, the study is inadequate for determining the potential carcinogenicity of TDCPP.

For the purposes of chracterizing cancer risk, an inhalation unit risk of $1.71 \times 10^{-5}/\mu g/m^3$ was estimated using Equation 16 in Chapter 3 and the oral cancer potency factor for TDCPP.

Oral

The available animal data on TDCPP provide sufficient evidence of carcinogenicity in rats following chronic oral exposure. Statistically significant and dose-dependent increases in the incidence of renal cortical tumors and liver adenomas were observed in male and female Sprague-Dawley rats chronically exposed to TDCPP in the diet for 2 yr (Bio/dynamics 1981). In addition, the incidence of adrenal cortical tumors in females and the incidence of interstitialtesticular cell tumors were significantly increased. Also in this study, there was a dose-related but not statistically significant increase in the incidence of liver carcinomas in animals exposed to TDCPP in the diet for 2 yr.

In vitro data suggest that TDCPP is a mutagen in the presence of liver S9 fraction, initiates DNA repair, and is clastogenic. These findings suggest that TDCPP (or one or more of its major metabolites), is DNA-reactive. Therefore, the subcommittee concluded that linear extrapolation is appropriate for estimating cancer risk in the low dose range.

Doses associated with a 10% increase in cancer risk were calculated for TDCPP using data for various tumor types with increased incidence reported in the Bio/dynamics (1981) study (Table 16–8). Cancer-potency estimates ($0.1/LED_{10}$) for TDCPP range from 0.01 to 0.06/mg/kg-d with the highest risk calculated for testicular tumors. It is debatable whether this tumor-type is caused by a mode of action relevant to humans (Akzo Nobel 1998, as cited in CPSC 1999). However, the subcommittee concluded that use of the cancer-potency estimate of 0.06/mg/kg-d for calculating TDCPP cancer risk is the most health-protective approach.

EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

Noncancer

Dermal

Dermal exposure to TDCPP was estimated using the dermal exposure scenario described in Chapter 3. This exposure scenario assumes that an adult

spends 1/4th of his or her time sitting on furniture upholstery backcoated with TDCPP and also assumes 1/4th of the upper torso is in contact with the upholstery and clothing presents no barrier. Exposure to other chemicals present in the backcoating was not included in this assessment.

TABLE 16–8 Calculated ED10, LED10, 0.1/ED10, and 0.1/LED10's for Tris(1,3-dichloropropyl-2) Phosphatea

Tumor type	ED_{10} (mg/kg-d)	LED_{10} (mg/kg-d)	$0.1/LED_{10}$	$0.1/ED_{10}$
FEMALES				
Adrenal cortical tumors	14.74	9.21	0.011	0.0068
Kidney cortical tumors	4.21	2.90	0.035	0.024
Liver adenoma	13.95	8.42	0.048	0.0072
Liver adenoma/carcinoma combined	9.21	6.05	0.017	0.011
MALES				
Testes interstitial cell tumor	1.84	1.58	0.063	0.054
Kidney cortical tumors	3.95	2.37	0.042	0.025
Liver adenoma	13.95	8.95	0.011	0.0072
Liver adenoma/carcinoma combined	11.05	5.26	0.019	0.0090

ED_{10}, effective dose corresponding to a 10% tumor response in test animals; LED_{10}, lower 95% bound on the effective dose corresponding to a 10% tumor response in test animals.
[a]Values calculated using tumor data from Bio/dynamics (1981).

First Iteration

As a first estimate of exposure, it was assumed that skin, clothing, and the upholstery did not impede dermal exposure to TDCPP present in the back-coating. It was also assumed that there would be sufficient water present from sweat to facilitate dissolution of TDCPP from the backcoating and absorption through the skin. In this scenario, only the dissolution rate of TDCPP from the backcoating is assumed to be the limiting factor in absorption by the body. It is assumed that all of the TDCPP that dissolves is immediately absorbed into the body by the sitting person.

Dermal exposure was estimated using Equation 1 in Chapter 3. For this calculation, the subcommittee estimated an upholstery application rate (S_a) for TDCPP of 5 mg/cm^2. The extraction rate (μ_w) for TDCPP was estimated to be 0.038 based on extraction data for organic phosphates in polyester fiber

(McIntyre et al. 1995). The release rate from the fiber for estimating extraction was 0.06/d at 28°C calculated using the equation $2d/2\ \pi R$ (d=film thickness, R=fiber radius) with a correction from fiber to film of a factor of 0.63.

Using these assumptions, an estimated absorbed daily dose of 1.5 mg/kg was calculated for TDCPP. A hazard index of 300 was calculated for this first iteration by dividing the estimated daily dermal dose of 1.5 mg/kg-d by the oral RfD for TDCPP of 0.005 mg/kg-d. At this time, the oral RfD is the best estimate of the internal dose associated with dermal exposure to TDCPP. These results suggest that TDCPP could be a toxic hazard if all available TDCPP is absorbed simultaneously.

Alternative Iteration

The estimated dermal daily dose for TDCPP can be calculated using an estimate of the dermal penetration rate for TDCPP (Chapter 3: Equations 2 and 3). Instead of assuming that all dissolved TDCPP immediately penetrates the skin and enters systemic circulation, it is assumed that the skin slows the absorption of TDCPP to a specific amount of chemical absorbed per unit of time. This estimate can be measured experimentally and is referred to as the skin permeability coefficient K_p. However, the dermal penetration constant for TDCPP has not been measured experimentally. However, K_p can be estimated from a correlation between the octanol-water partition coefficient (K_{ow}) and molecular weight (mass/unit amount of substance) using Equation 2 in Chapter 3 yielding an alternate K_p of 4.76×10^{-2} cm/d.

Using Equation 3 in Chapter 3 and the alternate K_p, the dermal daily dose rate for TDCPP was estimated to be 2.6×10^{-3} mg/kg-d. A hazard index of 0.52 was calculated by dividing the estimated daily dermal dose of 2.6×10^{-3} mg/kg-d by the oral RfD for TDCPP of 0.005 mg/kg-d. At this time, the oral RfD is the best estimate of the internal dose associated with dermal exposure to TDCPP. These results suggest that TDCPP is not anticipated to be a toxic risk by the dermal route at the stated application concentrations and under the given worst-case exposure conditions.

Inhalation Exposure

Particles

Inhalation exposure estimates for TDCPP were calculated using the exposure scenario described in Chapter 3. This scenario assumes that a person spends 1/4th of their life in a 30 m^3 room containing 30 m^2 of TDCPP-treated fabric

and the room is assumed to have an air-change rate of 0.25/hr. It is also assumed that 50% of the TDCPP present in 25% of the surface area of the treated fabric is released over 15 yr and 1% of released particles are a size that can be inhaled.

Particle exposure was estimated using Equations 4 and 5 in Chapter 3. The subcommittee estimated an upholstery application rate (S_a) for TDCPP of 5 mg/cm^2. The release rate (μ_r) for TDCPP from upholstery fabric was estimated to be 2.3×10^{-7}/d (see Chapter 3, Equation 5) yielding a room airborne particle concentration (C_p) of 1.9 µg/m3 and a short time-averaged exposure concentration of 0.48 µg/m^3. The time-averaged exposure concentration for particles was calculated using Equation 6 in Chapter 3.

Division of the time-average exposure concentration of 0.48 µg/m^3 by the provisional RfC for TDCPP of 0.018 mg/m^3 gives a hazard index of 2.7×10^{-2}. This suggests that under the subcommittee's worst-case exposure assumptions, TDCPP would not be considered a toxic hazard by the inhalation route of exposure.

Vapors

In addition to the possibility of release of TDCPP in particles from worn upholstery fabric, the subcommittee considered the possibility of the release of TDCPP by evaporation. This approach is described in Chapter 3, and uses an exposure scenario similar to that just described for exposure to TDCPP particles.

The rate of flow of TDCPP vapor from the room is calculated using Equation 8–11 in Chapter 3. A saturated vapor concentration (C_v) of 230 mg/m^3 was estimated for TDCPP. The application density (S_a) for TDCPP in the treated upholstery was estimated as 5 mg/cm^2.

Using the parameters described, the equilibrium room-air concentration of TDCPP was estimated to be 200 mg/m^3. The short-term time-average exposure concentration for TDCPP was estimated as 50 mg/m^3 using Equation 12 in Chapter 3 and the equilibrium room-air concentration for TDCPP. It was estimated that concentration could be maintained for approximately 1 mo.

These results indicate that if all of the TDCPP is released from the fabric into the air, TDCPP could be a toxic risk to persons entering the room. In reality, any flame retardant that evaporated so rapidly would be useless in preventing upholstery flammability. Either TDCPP is much more strongly bound to the fabric than assumed in this scenario (so that the parameter γ in the analysis above is substantially less than unity), or the chemical is transformed during the application process. In either case, the emission rate would likely be controlled by some process other than diffusion through a boundary layer of air, as as

sumed here. It is in the opinion of the subcommittee that this exposure scenario provides no useful information about the potential toxicity of TDCPP vapors to humans associated with the emission of TDCPP vapors from treated furniture upholstery. Therefore, further investigation should be carried out to determine if exposure to TDCPP by this route poses a toxic risk to humans.

Oral Exposure

The assessment of noncancer toxicological risk for oral exposure to TDCPP is based on the oral exposure scenario described in Chapter 3. This scenario assumes a child is exposed to TDCPP by sucking on 50 cm^2 of fabric backcoated with TDCPP, 1 hr/d for two yr. The subcommittee estimated an upholstery application rate (S_a) for TDCPP of 5 mg/cm^2. Oral exposure was calculated using Equation 15 in Chapter 3. The extraction rate (μ_w) for TDCPP was estimated to be 0.038 based on extraction data for organic phosphates in polyester fiber (McIntyre et al. 1995). The release rate from the fiber for estimating extraction was 0.06/d at 28°C calculated using the equation $2d/2\ \pi R$ (d=film thickness, R=fiber radius) with a correction from fiber to film of a factor of 0.63.

The worst case average oral daily dose for TDCPP was estimated as 0.04 mg/kg-d. Division of the dose estimate by the oral RfD for TDCPP of 0.005 mg/kg-d gives a hazard index of 8.0. This suggests that under the subcommittee's worst-case exposure assumptions, TDCPP could be a toxic hazard by the oral route of exposure.

Cancer

Dermal

Human cancer risk for dermal exposure to TDCPP was calculated by multiplying the oral cancer potency factor for TDCPP by the lifetime average dermal dose rates of 1.5 mg/kg-d or 2.6×10^{-3} mg/kg-d (see Noncancer Dermal Exposure section). The subcommittee felt that the use of the oral cancer potency factor for TDCPP based on testicular tumors in rats was acceptable for the calculation of cancer risk for dermal exposure since the oral cancer potency factor is based on carcinogenic effects following near-complete systemic absorption and the appearance of tumors not at the site of TDCPP application.

A lifetime cancer risk of 9.0×10^{-2} was obtained by multiplying the first iteration exposure estimate of 1.5 mg/kg-d times the TDCPP oral cancer potency factor of 0.06 mg/kg-d. Multiplication of the oral cancer potency factor

times the average dermal daily dose of 2.6×10^{-3} mg/kg-d developed in the alternative dermal exposure iteration gives an estimated lifetime cancer risk of 1.6×10^{-4}. These estimates suggest that the dermal route of exposure may pose a carcinogenic hazard for persons exposed to TDCPP incorporated into residential furniture upholstery at the indicated concentration levels and under the given worst-case exposure scenario.

Inhalation

Particles

The average room-air concentration and average exposure concentration to TDCPP particles estimated in the previous sections were used for the cancer assessment. An inhalation cancer potency value was not available for TDCPP, therefore a provisional inhalation cancer potency value was derived from oral cancer potency data for TDCPP. Multiplication of the exposure estimates of 0.48 μg/m^3 for particles times the provisional cancer potency value of 1.71×10^{-5}/μg/m^3 produces estimated lifetime cancer risks of 8.2×10^{-6} and suggests that the cancer risk associated with the inhalation of TDCPP particles is negligible at the given upholstery concentrations and the exposure parameters in the worst-case exposure scenario. However, the subcommittee noted that exposure to TDCPP by this route may need further evaluation.

Vapors

For TDCPP vapors, the equilibrium concentration of vapor-phase TDCPP in room air was estimated as described in the Noncancer Inhalation Exposure section. The long-term time-average vapor exposure concentration for TDCPP was estimated using Equation 14 in Chapter 3.

Oral

As discussed previously, TDCPP is judged to be a rodent carcinogen. Therefore, the conservative approach for risk assessment purposes is to assume that TDCPP represents a carcinogenic risk to humans.

Using Equation 16 in Chapter 3, the lifetime average dose rate for TDCPP by the oral exposure route was calculated to be 1.1×10^{-3} mg/kg-d. Lifetime cancer risk for this exposure scenario was then estimated by multiplying the oral lifetime daily dose rate times the most conservative oral cancer potency

factor for TDCPP (0.06/mg/kg-d) yielding a cancer risk estimate of 6.6×10^{-5}. This suggests that under the subcommittee's worst-case exposure assumptions, TDCPP could be a carcinogenic hazard by the oral route of exposure.

RECOMMENDATIONS FROM OTHER ORGANIZATIONS

The subcommittee is not aware of exposure limits proposed by regulatory agencies or other organizations.

DATA GAPS AND RESEARCH NEEDS

There are no data on the chronic toxicity of TDCPP by the dermal or inhalation routes of exposure. Data on the rate of dermal absorption of TDCPP are needed and there is no information on the metabolism of TDCPP in animal or human systems. No information is available on human exposure to TDCPP from treated furniture upholstery. No studies have been conducted on the leaching of TDCPP from treated materials.

Based on an oral hazard index of greater than 1 and potential cancer risk from all three routes of exposure, the subcommittee recommends that the potential for particle and vapor release and TDCPP release into saline from treated fabric be investigated.

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