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CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam*

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This report was prepared by the CPSC staff; it has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

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Summary

The U.S. Consumer Product Safety Commission (CPSC) staff developed a draft performance standard to address the hazards associated with fires involving residential upholstered furniture. Manufacturers are likely to treat some products with flame retardant (FR) chemicals if the draft standard is adopted. The CPSC staff previously assessed the potential health risks associated with the use of FR chemicals in upholstered furniture cover fabrics. In this report, the CPSC staff presents a preliminary assessment of the potential health risks associated with the use of selected FR chemicals in upholstered furniture foam. FR-treated foam samples that were available to the CPSC staff for testing included those with three different FR chemicals or mixtures that could be used to meet the draft standard: melamine (108-78-1); tris(1,3-dichloro-2-propyl)phosphate (TDCP) (13674-87-8); and Firemaster™ 550 (FM-550™). FM-550™ is a mixture containing triphenyl phosphate (TPP) (1145-86-6), phenol isopropylated phosphate (PIP) (68937-41-7), and octyl tetrabromobenzoate (OTB). Samples with the highest available TDCP or FM-550™ levels were included in the study. Numerous other FR treatments that could be used in foam have been discussed by the U.S. Environmental Protection Agency's (EPA's) Design for the Environment Program.

The toxicity of FR chemicals was assessed according to the Federal Hazardous Substances Act (FHSA), the supplemental definition of "toxic," and the CPSC chronic hazard guidelines. Although melamine has been studied in chronic bioassays, it does not satisfy the FHSA definition of toxic. Thus, exposure studies with melamine-treated foam were not necessary. Based on the available data, melamine-treated foam would not present a hazard to consumers. TDCP is considered a probable human carcinogen, based on sufficient evidence in animal studies. TDCP also induces non-cancer chronic health effects in animals. Little toxicity information on FM-550™ and its components is available. However, the CPSC staff has previously reviewed the toxicity of two FM-550™ components, TPP and PIP, as well as closely related compounds. No toxicity data were available for OTB.

Mock-ups made with the foam samples were tested by the staff to assess the liquid-mediated migration of FR chemicals. These data were used to estimate dermal and oral exposures. The mock-ups were also subjected to an accelerated wear procedure to measure the release of airborne particles containing FR chemical. Two foam samples containing TDCP and one containing FM-550™ were tested. Measurements of migration and particle release from FM-550™-treated foam were based on the OTB component. The other components were not measured. Exposure to vapor phase chemicals that may be emitted from the foam was assessed using a mathematical model.

Based on the CPSC staff's analysis, it appears that inhalation of vapor phase FR chemical contributes the greatest portion of the total exposure. However, a mathematical model was used to estimate inhalation exposure due to the lack of empirical data. Thus, the estimated inhalation exposure is highly uncertain. Toxicity studies by the inhalation route are also lacking. Therefore, the following conclusions are based on limited exposure and/or toxicity data, and should be regarded as preliminary.

Most of the predicted exposure to TDCP is from the inhalation of TDCP, which was estimated from a mathematical model. Regarding non-cancer health effects, estimated TDCP exposures were above the acceptable daily intake (ADI). The hazard index (HI) values were 2 for adults and 5 for children. When the estimated exposure exceeds that ADI a substance may be considered "hazardous," as defined in the CPSC chronic hazard guidelines and FHSA regulations. 16 CFR 1500.135 and 16 CFR 1500.3 (c)(2). The estimated cancer risk for a lifetime of exposure to TDCP-treated upholstered furniture was 300 per million. In children, the estimated cancer risk from exposure during the first two years of life alone was 20 per million. Both of these risks exceed one-in-a-million. A substance may be considered hazardous if the lifetime individual cancer risk exceeds one-in-a-million (*ibid.*). However, empirical measurements of TDCP emissions, which were not available for this study, are needed to assess more definitively whether TDCP may present a hazard to consumers.

Limited toxicity data are available for TPP and PIP. Thus, the range of ADI values for other aromatic phosphates or blends previously reviewed by the CPSC staff was used as a surrogate. Using these surrogate toxicity data, HI values for TPP were estimated to be between 0.002 and 0.2 in adults and between 0.005 and 0.5 in children. The HI's for PIP were about 10-fold lower. If TPP and PIP are not more toxic than the other aromatic phosphates, then TPP and PIP are not expected to pose any appreciable health risk to consumers. The staff will review any additional toxicity data on TPP and PIP that may become available. Additional toxicity data and measurements of TPP and PIP emissions are needed to assess more definitively whether these compounds may present a hazard to consumers. Measurements of the TPP and PIP components of FM-550™ are needed to reduce the uncertainty in estimating exposure. The CPSC staff has requested the National Toxicology Program to perform additional toxicity tests on aromatic phosphates.

Insufficient toxicity data on OTB, another component of FM-550™, or related compounds were available to assess whether OTB could present a hazard to consumers. Basic toxicity data, physico-chemical data, and additional exposure data are needed to assess whether OTB may be hazardous to consumers.

In summary, the staff concludes that:

- Based on the available data, melamine-treated foam is not expected to present a hazard to consumers.
- Inhalation studies are lacking for TDCP, TPP, PIP, and OTB. This is significant because inhalation appears to contribute the greatest portion of the total exposure.
- Empirical data on vapor phase emissions or indoor concentrations are needed to assess whether TDCP, TPP, PIP, or OTB may present a hazard to consumers.
- Chemical-specific migration and release data are needed to assess more accurately whether TPP and PIP may present a hazard to consumers.
- Additional toxicity data are needed to derive ADI values for TPP and PIP.
- Basic toxicity and physico-chemical data for OTB are needed to derive an acceptable daily intake value and to estimate exposure.

Abbreviations

ADD	Average daily dose
ADI	Acceptable daily intake
AFSC	American Fire Safety Council
APP	Aromatic phosphate plasticizer
AT	Antimony trioxide
BMD	Benchmark dose
CAR	Constitutively active receptor
CPSC	U.S. Consumer Product Safety Commission
DBDPO	Decabromodiphenyl oxide
DfE	Design for the Environment (U.S. EPA)
ED_{50}	Median effective dose
EHDP	2-Ethylhexyl diphenyl phosphate
EPA	Environmental Protection Agency (U.S.)
FHSA	Federal Hazardous Substances Act
FM-550™	Firemaster™ 550
FR	Flame retardant
FRCA	Fire Retardant Chemicals Association (currently AFSC)
GD	Gestational day
HBCD	Hexabromocyclododecane
HI	Hazard index
IC_{50}	Concentration at 50% inhibition
IDDP	Isodecyl diphenyl phosphate
IPDP	Isopropylphenyl diphenyl phosphate
K_{OW}	Octanol-water partition coefficient
LADD	Lifetime average daily dose
LD_{50}	Median lethal dose
LOAEL	Lowest-observed-adverse-effect level
MSDS	Material safety data sheet
NOAEL	No-observed-adverse-effect level
NRC	National Research Council
NTE	Neurotoxic esterase
NTP	National Toxicology Program
OPIDN	Organophosphate induced delayed neurotoxicity
OTB	Octyl tetrabromobenzoate
PA	Phosphonic acid, (3-{[hydroxymethyl]amino}-3-oxopropyl)-, dimethyl ester
Penta-BDE	Pentabromodiphenyl ether
PIP	Phenol isopropylated phosphate
PUF	Polyurethane foam
PXR	Pregnane X receptor
RfD	Reference dose
SCE	Sister chromatid exchange
SD	Sprague-Dawley
SNUR	Significant new use rule

Abbreviations (continued)

TCP	Tricresyl phosphate
TDCP	Tris(1,3-dichloro-2-propyl)phosphate
THPC	Tetrakis(hydroxymethyl)phosphonium chloride
TPP	Triphenyl phosphate
TRIS	Tris(2,3-dibromopropyl)phosphate
UDS	Unscheduled DNA synthesis
UF	Uncertainty factor
VCCEP	Voluntary Children's Chemical Evaluation Program

I. INTRODUCTION

Upholstered furniture fires account for more fire deaths than any other category of products under the jurisdiction of the U.S. Consumer Product Safety Commission (CPSC). The staff estimates that an annual average of 4,800 fires, 360 deaths, 740 injuries, and $133 million in property damage would be addressed if the draft standard is enacted (Levenson 2005). These fires are most commonly ignited by either smoldering sources, such as cigarettes, or open flame sources, such as cigarette lighters and candles. CPSC initiated a regulatory proceeding to address the hazard of small open flame ignitions of upholstered furniture (CPSC 2003). The CPSC staff has developed a draft performance standard to address the hazards associated with both small open flame and cigarette ignitions.

While furniture manufacturers would be free to choose the means of complying with the draft standard, it is likely that some products would be treated with flame retardant (FR) chemicals if the draft standard were adopted. In addressing the hazard associated with the flammability of upholstered furniture, the CPSC staff is working to develop a performance standard to reduce furniture fires without creating other hazards to consumers. Thus, the CPSC staff has been assessing the potential for health risks associated with the use of selected FR chemicals in upholstered furniture. The purpose of this report is to assess the potential health risks associated with the use of selected FR chemicals in upholstered furniture foam.

A. Upholstered Furniture Cover Fabrics

The first version of the draft flammability standard developed by the CPSC staff involved exposing the upholstered furniture cover fabric to a gas flame that was roughly equivalent to that of a cigarette lighter (CPSC 1997). As part of the risk assessment process for FR chemicals, the Commission held a public hearing in May 1998. In its testimony, the Fire Retardant Chemicals Association (FRCA) (currently the American Fire Safety Council, AFSC) reported that in many cases the furniture cover fabric would be treated with FR chemicals if the draft standard were adopted (Parkes 1998). The FRCA also provided a list of 16 chemicals or chemical classes that its members would market for use in upholstered furniture.

The 16 FR chemicals and classes included over 50 individual compounds. The CPSC staff reviewed all the available toxicity data on these chemicals and derived acceptable daily intake (ADI) levels where sufficient data were available (Babich et al. 2004; Babich and Saltzman 1999; Bittner 1999a-d; Bittner 2001; Bittner et al., 2001; Bittner and Ferrante, 1999; Ferrante 1999a-f; Hatlelid 1999a-h). Overall, a considerable number of toxicological studies were available for review. While some FR chemicals have been well studied, only limited data were available for others.

The CPSC staff performed quantitative risk assessments for five FR chemicals: antimony trioxide (AT) (CAS no. 1309-64-4); decabromodiphenyl oxide (DBDPO) (1163-19-5); hexabromocyclododecane (HBCD) (3194-55-6); phosphonic acid, (3-{[hydroxymethyl]amino}-3-oxopropyl)-, dimethyl ester (PA) (20120-33-6); and tetrakis (hydroxymethyl) phosphonium chloride (THPC) (124-64-1) (Babich and Thomas 2001). These FR's were selected for study because they are used to comply with the U.K. upholstered furniture flammability standard

(except THPC) and fabric samples were available for testing. The staff concluded that DBDPO, HBCD, and PA would not present a hazard to consumers, and that additional data would be needed to assess AT and THPC.

Prior to the completion of the CPSC staff risk assessment, the National Research Council (NRC) performed a risk assessment of 16 FR chemicals that might be used in upholstered furniture cover fabrics (NRC 2000). The NRC subcommittee, which had minimal exposure data available to them, selected the most toxic chemical to represent each of the same 16 chemicals or classes described by the FRCA. The NRC concluded that eight of these chemicals could be used without presenting a hazard to consumers, including DBDPO, HBCD, PA, and THPC. They also concluded that additional exposure or toxicity data were needed for the remaining chemicals, including AT, tris(1,3-dichloro-2-propyl) phosphate (TDCP), and aromatic phosphate plasticizers. Following the completion of the NRC report, the CPSC staff found that unidentified compounds were released from THPC-treated fabrics. Thus, the staff concluded that additional information on the identity and toxicity of the THPC by-products was needed.

The CPSC staff is participating in several regulatory and voluntary programs of the U.S. Environmental Protection Agency (EPA) that involve the potential health and environmental effects of FR chemicals. EPA is developing a significant new use rule (SNUR) for FR chemicals that may be used in upholstered furniture. A SNUR requires manufacturers to notify EPA before engaging in activities subject to the SNUR. The SNUR process can be used to obtain additional toxicity or exposure data if needed. The EPA Design for the Environment (DfE) program is a cooperative effort with industry that is evaluating the potential health risks of FR chemicals that may be used in polyurethane foam (PUF). The EPA Voluntary Children's Chemical Evaluation Program (VCCEP) is investigating children's exposure to penta- and octa-bromodiphenyl ether and DBDPO.

B. Upholstered Furniture Foam

In 2003, the Commission amended the rulemaking activity for upholstered furniture to include smoldering ignition sources, such as cigarettes, and the staff revised the draft performance standard (CPSC 2003). Due to the changes in the draft flammability standard, fewer upholstery cover fabrics are likely to be treated with FR chemicals if the standard is adopted. Rather, in many cases the flexible PUF or other filling materials may require FR treatment to meet the draft standard.

Until recently, mixtures containing pentabromodiphenyl ether (penta-BDE) and aromatic phosphate esters were the principal FR chemicals for flexible PUF. However, the sole U.S. manufacturer of penta-BDE voluntarily ceased production in December 2004 due to concerns about environmental persistence and bioaccumulation. A number of alternative treatments are available, including several new proprietary formulations (reviewed in EPA 2005a). FR treatments that may be used in upholstered furniture foam include tris(1,3-dichloro-2-propyl) phosphate (TDCP) (13674-87-8), melamine (108-78-1), and a proprietary formulation marketed as Firemaster™ 550 (FM-550™) (Figure 1). FM-550™ is a mixture containing triphenyl phosphate (TPP) (1145-86-6), phenol isopropylated phosphate (PIP) (68937-41-7), and octyl

tetrabromobenzoate (mixture of isomers) (OTB) (CAS no. not available) (EPA 2005a).* According to its material safety data sheet (MSDS) (Great Lakes 2005), FM-550™ contains 6-24% TPP, 24-51% PIP, and 40-60% OTB. Melamine may be blended with other FR's, including TDCP. Several other alternative FR chemicals for use in PUF are mixtures that include various aromatic phosphates. This report will assess the potential chronic health risks associated with the use of TDCP, FM-550™, and melamine in upholstered furniture foam.

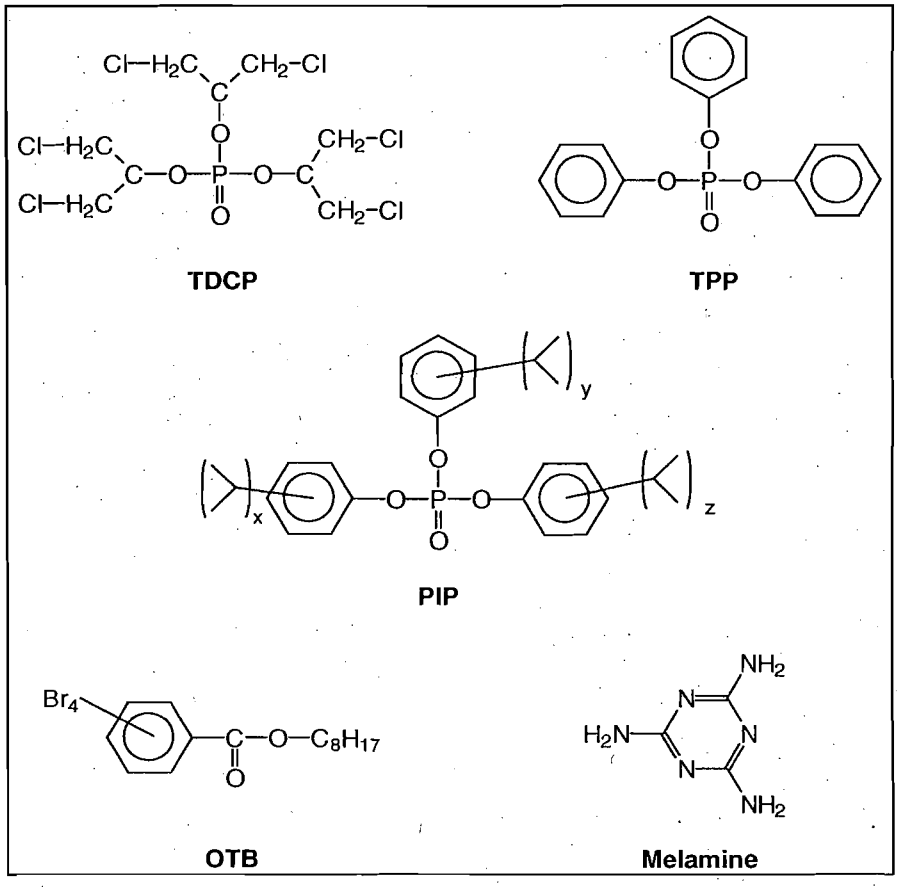

Figure 1. Structures of FR Chemicals

C. Risk Assessment and the Federal Hazardous Substances Act

CPSC addresses chemical hazards under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a substance or product must satisfy a two-part definition. 15 USC 1261 (f)(1)(A). First, it must be "toxic" as defined under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial illness or injury" during or as a result of

* Some of the abbreviations used in the January 2006 draft of this report were changed to reflect new information that more specifically identifies certain chemicals. BAE (brominated aryl ester) was changed to OTB (octyl tetrabromobenzoate) and ITP (isopropylated triphenyl phosphate) was changed to PIP (phenol isopropylated phosphate).

"reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC, 1992).

The first step in the risk assessment process is hazard identification, that is, to review the available toxicity data for each chemical under consideration and determine whether the chemical is "toxic" under the FHSA. Acute toxicity is defined by LD_{50} (median lethal dose) values in regulations issued under the FHSA. 16 CFR 1500.3 (c) (2) (i). However, reliable human experience data take precedence over animal data. 16 CFR 1500.4. In 1992, the Commission issued guidelines for assessing chronic hazards under the FHSA, including carcinogenicity, neurotoxicity, reproductive and developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk (CPSC, 1992; summarized at 16 CFR 1500.135). A substance is considered "toxic" under the FHSA due to chronic toxicity if it is either known to be, or probably, toxic in humans. 16 CFR 1500.3 (c)(2)(ii). Under the FHSA, a substance or mixture is classified as "known to be toxic" in humans only if there is sufficient evidence in humans (Table 1). It is considered "probably toxic" if there is either limited evidence in humans or sufficient evidence in animals.

Table 1. Classification of Chronic Hazards under the FHSA

	Humans	Animals
Sufficient Evidence	Known*	Probable*
Limited Evidence	Probable*	Possible
Inadequate Evidence	Possible	---

* Satisfies the regulatory definition of "toxic."

If a substance is "toxic" under the FHSA due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to determine whether the chemical may be a "hazardous substance" under the FHSA. The quantitative risk assessment includes a consideration of dose response, bioavailability, and exposure.

The acceptable daily intake (ADI) and/or cancer unit risk are derived from appropriate dose-response information, and the exposure is estimated. If the estimated exposure exceeds the ADI or if the estimated cancer risk is greater than one-in-a-million then the substance may be considered a "hazardous substance" (CPSC 1992). 16 CFR 1500.3 (c)(2)(ii).

II. HAZARD

A. Tris(1,3-Dichloro-2-Propyl)Phosphate (TDCP)

The toxicity of tris(1,3-dichloro-2-propyl)phosphate (TDCP) has been reviewed by the CPSC staff (Bittner et al. 2001; Ferrante 1999b; Ulsamer et al. 1980) and others (Brandwene 2001; EPA 2005a; IPCS 1998; NRC 2000). The toxicity of TDCP is summarized below (see Table 2).

TDCP is a viscous liquid with molecular weight 430.9, log K_{ow} 3.8, vapor pressure 0.01 torr, and low water solubility (reviewed in IPCS 1998). Oral LD_{50} values ranged from 2.36 to 3.16 g/kg in rats and from 2.25 to 4.99 mL/kg in mice (reviewed in Ferrante 1999b). The symptoms associated with acute exposure included ataxia, irritability, hyperactivity, tetanus, and convulsions, suggesting neurological effects. TDCP was not a sensitizer in guinea pigs. It was either a non-irritant or mild irritant in the skin and eyes of rabbits (Stauffer 1981).

1. Genotoxicity

TDCP was either inactive or weakly mutagenic in *Salmonella* strain TA100 (Brusick et al. 1980; Gold et al. 1978; Nakamura et al. 1979; Prival et al. 1977; Soderlund et al. 1985; Stauffer 1981) and inactive in yeast (Stauffer 1981). Negative results that were reported in some studies (Brusick et al. 1980; Prival et al. 1977; Soderlund et al. 1985; Stauffer 1981) may be due to the method of metabolic activation (Brusick et al. 1980; Gold et al. 1978; Nakamura et al. 1979; Soderlund et al. 1985). The major urinary metabolite of TDCP, bis(1,3-dichloro-2-propyl) phosphate, was not mutagenic (Gold et al. 1978). However, another metabolite, 1,3-dichloro-2-propanol, was reported to be weakly mutagenic. In addition, the putative metabolite 1,3-dichloro-2-propanone was a strong direct-acting mutagen. TDCP was less mutagenic than the structural analog tris(2,3-dibromopropyl) phosphate (TRIS) (Brusick et al. 1980; Nakamura et al. 1979).

TDCP generally gave weak or negative results in mammalian systems. TDCP transformed Syrian hamster embryo cells (Soderlund et al. 1985), but not Balb 3T3 cells (Brusick et al. 1980; Stauffer 1981), *in vitro*. TDCP was weakly active in several *in vitro* assays, including the induction of forward mutations (thymidine kinase), sister chromatid exchanges, and chromosomal aberrations. TDCP did not induce 6-thioguanine resistance in V79 cells, nor did it induce unscheduled DNA synthesis in rat hepatocytes, although TRIS was active at similar doses (Soderlund et al. 1985).

TDCP failed to induce chromosomal aberrations in mouse bone marrow cells *in vivo* (Brusick et al. 1980; Stauffer 1981). TDCP failed to induce unscheduled DNA synthesis in rat hepatocytes, following oral exposure at doses up to 2,000 mg/kg (Cifone 2005), and did not induce micronuclei in mice (Thomas and Collier 1985). TDCP was reported to bind to DNA and proteins in mice exposed *in vivo* (Morales and Matthews 1980).

Table 2. Chronic Health Effects of Selected Flame Retardant Chemicals [a]

Chemical	Availability of Toxicity Data							Chronic Health Effects				
	Acute	Subchronic	Chronic	Repro/Dev	Neurotox	Genetox	Human	Chronic Toxicity [b]	Endpoint [c]	NOAEL/LOAEL [d] (mg/kg-d)	UF [d]	ADI [d] (mg/kg-d)
Aromatic phosphate plasticizers (APP's):												
Phenol isopropylated phosphate (PIP)	X [e]	X	—	—	X	—	X	C	N,O			ND [e]
Triphenyl phosphate (TPP)	X	X	—	X	X	X	X	C	O			ND
t-Butylphenyl diphenyl phosphate (BPDP)	—	X	—	—	X	X	X	I				ND
2-Ethylhexyl diphenyl phosphate (EHDP)	X	X	X	X	X	X	—	B	O	100	100	1.0
Isodecyl diphenyl phosphate (IDDP)	X	X	—	—	X	X	—	C	O			ND
Santicizer 141 (>90% EHDP)	X	X	—	X	X	X	—	B	O	100	100	1.0
Santicizer 148 (> 90% IDDP)	X	X	—	X	X	X	—	B	O			0.01
Santicizer 154 (TPP + BPDP)	X	X	—	X	X	X	—	C	N,O			ND
o-Tricresyl phosphate (o-TCP)	X	X	—	X	X	—	X	A	N			ND
Tricresyl phosphate (TCP) (isomers)	X	X	X	X	X	X	X	B	R,N,O	50 L [e]	1,000	0.05
Melamine (1,3,5-triazine-2,4,6-triamine)	X	X	X	X	—	X	—	C	C			ND
Octyl tetrabromobenzoate (OTB)	X	—	—	—	—	—	—	I				ND
Tris(1,3-chloropropyl-2) phosphate (TDCP)	X	X	X	X	X	X	—	B	C	5 L	1,000	0.005

[a] Adapted from Bittner et al. 2001.
[b] Chronic toxicity as defined by the FHSA and the CPSC chronic hazard guidelines: A, known to be toxic in humans; B, probably toxic in humans; C, possibly toxic in humans; I, insufficient data.
[c] Chronic endpoint(s): C, cancer; D, developmental; N, neurotoxic; R, reproductive; O, other (e.g., liver or other organ toxicity).
[d] ADI, acceptable daily intake; LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; UF, uncertainty factor.
[e] L, LOAEL; ND, not determined; X, data available.

2. Toxicokinetics

Ninety percent of orally administered [1,3-^{14}C]2-propyl-labeled TDCP was absorbed in rats (Matthews and Anderson 1979). The highest levels of TDCP were found in the kidney, liver, and lung (Matthews and Anderson 1979; Nomeir et al. 1981; Ulsamer et al. 1979, 1980). Eighty percent of TDCP was eliminated within 24 hours, primarily in the urine, in both rats and rabbits. From 9-to-15% was converted to CO_2. Bis(1,3-dichlor-2-propyl) phosphate was the primary metabolite in urine. Other metabolites included 1,3-dichloro-2-propanol and 3-chloro-1,2-propanediol (Figure 2). TDCP is also directly conjugated by glutathione, probably through one of the ester groups. It has been suggested that TDCP may also be metabolized to 1,3-dichloro-2-propanone, by analogy to TRIS (Gold et al. 1978), but this has not been observed.

In vitro studies suggest that TDCP is metabolized to the diester by an NADPH-dependent mixed function oxidase, as well as by glutathione conjugation (Nomeir et al. 1981; Sasaki et al. 1984). A glutathione-conjugated metabolite was also identified.

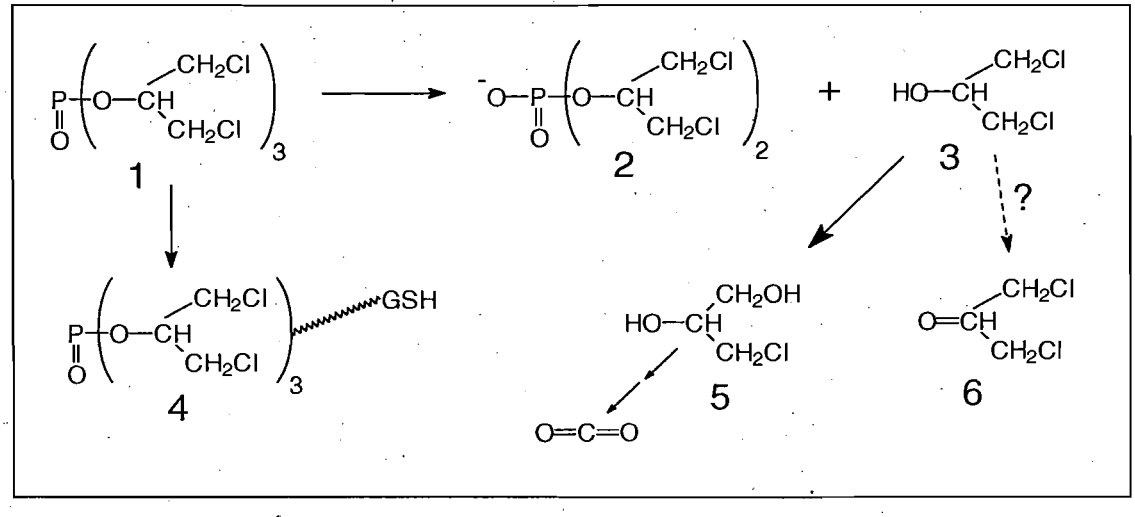

Figure 2. Metabolism of tris(1,3-dichloro-2-propyl)phosphate. Structures: 1) tris(1,3-dichloro-2-propyl)phosphate (TDCP); 2) bis(1,3-dichlor-2-propyl) phosphate; 3) 1,3-dichloro-2-propanol; 4) glutathione conjugate of TDCP; 5) 3-chloro-1,2-propanediol; 6) putative metabolite 1,3-dichloro-2-propanone. Sources: Lynn et al. 1981; Nomeir et al. 1981; Gold et al. 1978.

TDCP was rapidly absorbed through the skin in both rats and rabbits (Nomeir et al. 1981; Ulsamer et al. 1979, 1980). TDCP was absorbed at double the rate of tris(2,3-dibromopropyl)phosphate (Ulsamer et al. 1979). When ^{14}C-TRIS was applied to the clipped skin of New Zealand white rabbits, up to 15% of the applied dose was absorbed over 96 hours (Ulsamer et al. 1978a). Thus, TRIS was absorbed at a rate of 0.0016 h^{-1}. Nomeir et al. (1981) showed that TDCP is rapidly absorbed in rats, although the absorption rate was not determined.

Percutaneous absorption of ^{14}C-TDCP was also studied *in vitro* with hairless mouse skin (Hughes et al. 2001). After 24 hours, from 39-to-57% of applied TDCP was found in the receptor fluid. From 28-to-35% remained in the skin after the skin surface was washed with ethanol. From 73 to 85% of applied TDCP was absorbed in 24 hours. Combining the amounts

in the receptor fluid and skin, TDCP was absorbed at a rate up to 0.035 h^{-1} (Babich and Thomas 2001).

Five days following intravenous administration of ^{14}C-labeled TDCP in rats, 92% of the radiolabel was excreted (Lynn et al. 1981). Fifty-four percent of radiolabel was found in urine, 16% in feces, and 22% was expired as $^{14}CO_2$. The primary metabolite was bis(1,3-dichlor-2-propyl) phosphate, which accounted for 63% of the radiolabel. Other metabolites included 1,3-chloropropyl phosphate and 1,3-dichloro-2-propanol. Less than 0.1% of the radiolabel was recovered as TDCP.

3. Subchronic and Chronic Studies

Groups of 12 male and 12 female mice were fed up to 1.33% TDCP for 3 months (Kamata et al. 1989). All animals in the high-dose group died within one month. Liver weights were elevated in males at 0.13% and 0.42% and in females at 0.04%, 0.13%, and 0.42%. The overall study no-observed-adverse-effect level (NOAEL) was 0.01% (15 mg/kg-d) in females.

TDCP was studied in a 24-month dietary bioassay in Sprague-Dawley (SD) rats (Biodynamics 1981; Freudenthal and Henrich 2000; Henrich 1998).* Animals were exposed to TDCP in feed at doses of 0, 5, 20, or 80 mg/kg-d in groups of 60 per dose and sex. Ten animals from each dose-sex group were sacrificed at 12 months. Complete histopathology was performed on all high-dose animals, but only on a small number of animals at the low- and mid-doses. Liver and kidney were examined in all animals at all doses.

Non-cancer effects observed at terminal sacrifice included convoluted tubule hyperplasia in males at all doses and in high-dose females (Table 3) (reviewed in NRC 2000). The incidence of parathyroid hyperplasia was significantly elevated in high-dose males only. Erythroid/myeloid metaplasia of the spleen was significantly elevated in females at all doses; this is not considered a pre-neoplastic lesion. In addition, there were reproductive system lesions in males, including the seminal vesicles (atrophy and decreased secretory product, all doses), testes (periarteritis nodosa and eosinophilic material in the lumen, mid-and high doses), and epididymes (oligospermia and/or degenerated seminal product, mid- and high dose). Altered liver foci, which suggest the presence of initiated cells, were elevated only in high-dose females. The NRC subcommittee considered the low dose (5 mg/kg-d) as a lowest observed adverse effect level (LOAEL) (NRC 2000). TDCP may be considered probably toxic to humans (see CPSC 1992), based on sufficient evidence of chronic toxicity (histopathological effects at multiple organ sites) in animals.

* This study was first described in an unpublished report (Biodynamics 1981), which is also referred to as the "Stauffer Chemical Co. report." The tumorigenic effects were later published in (Freudenthal and Henrich 2000). Henrich (1998) provided additional discussion of tumor incidences.

Table 3. Incidence of Selected Histopathological Effects in Sprague-Dawley Rats Exposed to TDCP in Feed [a]

Tissue/Lesion	Sex		Dose (mg/kg-d) 0	5	20	80
Liver, altered foci	M	Incidence	22/60	20/60	16/60	31/60
		P [b, c]		0.42	0.16	0.071
	F	Incidence	16/60	23/60	18/55	36/60
		P		0.12	0.31	**2.1×10^{-4}**
Kidney, convoluted tubule hyperplasia	M	Incidence	2/60	10/60	29/60	24/59
		P		**0.015**	**4.3×10^{-9}**	**3.4×10^{-7}**
	F	Incidence	0/60	1/60	3/57	22/60
		P		0.50	0.11	**1.4×10^{-6}**
Spleen, erythroid/myeloid metaplasia	M	Incidence	13/60	3/6	4/6	17/58
				0.15	**0.034**	0.23
	F	Incidence	13/60	5/6	3/4	33/60
		P		**4.7×10^{-3}**	**0.045**	**1.6×10^{-4}**
Parathyroid, hyperplasia	M	Incidence	1/29	1/1	0/2	12/38
		P		0.067	0.94	**3.3×10^{-3}**
	F	Incidence	6/29	NR [c]	NR	9/28
		P				0.24
Testes, eosinophilic material in the lumen	M	Incidence	2/57	4/60	12/60	11/56
		P		0.36	**5.5×10^{-3}**	**7.1×10^{-3}**
Testes, periarteritis nodosa	M	Incidence	5/57	10/60	19/60	16/56
		P		0.16	**1.9×10^{-3}**	**6.2×10^{-3}**
Epididymes, oligospermia	M	Incidence	11/55	9/33	7/14	36/55
		P		0.30	**0.030**	**1.2×10^{-6}**
Epididymes, degenerated seminal product	M	Incidence	8/55	7/33	3/14	22/55
		P		0.30	0.39	**2.4×10^{-3}**
Seminal vesicle, decreased secretory product	M	Incidence	1/56	11/13	17/20	23/52
		P		**4.2×10^{-10}**	**4.0×10^{-13}**	**2.5×10^{-8}**
Seminal vesicle, atrophy	M	Incidence	0/56	4/13	6/20	10/52
		P		**8.3×10^{-4}**	**1.8×10^{-4}**	**4.1×10^{-4}**

[a] Data are from NRC 2000, Table 16-4. Includes only significantly elevated sites.
[b] One-tailed Fisher's exact test performed by CPSC staff. Probabilities <0.05 are in bold.
[c] NR, not reported; P, probability.

Table 4. Tumor Incidence in Sprague-Dawley Rats Exposed to TDCP in Feed [a]

			Dose (mg/kg-d)			
Tumor	**Sex**		**0**	**5**	**20**	**80**
Renal cortex tumor	M	Incidence	1/60	3/60	9/60	32/59
		P [b]		0.309	**$8.3x10^{-3}$**	**$1.1x10^{-11}$**
	F	Incidence	0/60	1/60	8/57	29/60
		P		0.500	**$2.4x10^{-3}$**	**$2.0x10^{-11}$**
Testicular interstitial cell adenoma	M	Incidence	7/57	8/60	26/60	39/56
		P		0.540	**$1.6x10^{-4}$**	**$2.5x10^{-10}$**
Hepatocelullar adenoma	M	Incidence	2/60	7/60	1/60	16/60
		P		0.081	0.878	**$2.7x10^{-4}$**
	F	Incidence	1/60	1/60	4/55	9/60
		P		0.752	0.156	**$8.3x10^{-3}$**
Hepatocellular carcinoma	M	Incidence	1/60	2/60	3/60	7/60
		P		0.500	0.309	**0.031**
	F	Incidence	0/60	2/60	2/55	4/60
		P		0.248	0.227	0.059
Hepatocellular adenoma or carcinoma	M	Incidence	3/60	9/60	4/60	23/60
		P		0.220	0.500	**$5.7x10^{-4}$**
	F	Incidence	1/60	3/60	6/55	13/60
		P		0.309	**0.044**	**$4.9x10^{-4}$**
Adrenal cortex adenoma	M	Incidence	5/59	3/14	5/16	5/57
		P		0.421	**0.031**	0.607
	F	Incidence	13/59	5/27	2/33	20/59
		P		0.740	**0.040**	0.109

[a] Tumor data are from NRC 2000, Table 16-5.
[b] One-tailed Fisher's exact test performed by CPSC staff. Probabilities (P) <0.05 are in bold.

Several neoplastic lesions were also reported (Biodynamics 1981; Freudenthal and Henrich 2000; Henrich 1998 and reviewed in EPA 2005a; Ferrante 1999b; NRC 2000). The incidence of renal cortical tumors was significantly elevated relative to the controls in mid- and high-dose males and females (Table 4). Benign testicular interstitial cell tumors were also significantly elevated in mid- and high-dose males. Hepatocellular adenomas were significantly elevated at the high dose in both sexes, while hepatocellular carcinomas were significantly elevated in high-dose males only. The incidence of hepatocellular adenoma or carcinoma was significantly elevated at the high dose in males and the mid- and high doses in females. Adenomas of the

adrenal cortex were significantly elevated in mid-dose males (not at the high dose) and significantly reduced in mid-dose females.

4. Reproductive and Developmental Toxicity

Groups of 10 male rabbits were given 0, 2, 20, or 200 mg/kg-d TDCP by gavage for 12 weeks (Wilczynski et al 1983; see also Brandwene 2001). No changes in mating behavior, fertility, or sperm quantity or quality were observed. Rabbits at the high dose had elevated kidney and liver weights. No histopathological effects were observed in the pituitary, testes, epididymes, liver, or kidneys. Other tissues were not examined.

Groups of 20 female rats were given 0, 25, 100, or 400 mg/kg-d TDCP by gavage on gestational days (GD's) 6 through 15 (Stauffer 1981). At GD 19, high-dose fetuses exhibited reduced viability, weight, and length. The incidences of resorption and incomplete ossification were also increased at the high dose. No malformations were reported. Signs of maternal toxicity included increased mortality at the high dose and decreased body weight and food consumption at the mid- and high doses.

In another developmental screen, Kawashima et al. (1983) gavaged female rats at doses of 0, 25, 50, 200, or 400 mg/kg-d on gestational days 7 through 15. Fetal deaths were observed at the high dose, but no malformations occurred. There were signs of maternal toxicity at 200 and 400 mg/kg-d, including decreased body weight and food consumption.

No malformations were observed in two developmental screening assays in rats (Kawashima 1983; Stauffer 1981; reviewed in Ferrante 1999a; NRC 2000). Fetal effects such as reduced viability and body weight, along with signs of maternal toxicity, were observed at the doses of 200 mg/kg-d or greater in both studies. The highest NOAEL in the developmental studies was 100 mg/kg-d. No effects on male fertility were observed in rabbits exposed to doses up to 200 mg/kg-d for 12 weeks (Wilczynski et al 1983). This is somewhat in contrast to the observation of histopathological effects in the testes at 5 mg/kg-d in the two-year bioassay in rats (Biodynamics 1981). However, the lesions in the chronic study did not appear until after the 12-month interim sacrifice.

5. Neurotoxicity

The neurotoxicity of TDCP was studied in hens. No signs of neurotoxicity or paralysis were reported at 420 mg/kg-d (by gavage) for 5 days (Stauffer 1981). TDCP was a weak inhibitor of brain neurotoxic esterase in hens given 10,000 mg/kg-d. Oral TDCP at 4,800 mg/kg was fatal in chickens, although lower doses (unspecified) resulted in leg and wing weakness (Celanese 1960). It does not appear that TDCP is capable of inducing organophosphate-induced delayed neurotoxicity (OPIDN) in hens (see below). Exposure of rats to TDCP at high doses lead to clinical signs suggestive of neurotoxicity, such as hyperactivity and convulsions (see above).

6. Toxicity under the FHSA

TDCP is acutely toxic, as defined in FHSA regulations, although it is not considered "highly" toxic.* That is, the rat LD_{50} is less than or equal to 5,000 mg/kg, but greater than 50 mg/kg. TDCP exposure led to histopathological effects in rats exposed for up to two years (Biodynamics 1981). Organ sites affected include the liver, kidney, spleen, parathyroid, and male reproductive organs. Thus, TDCP may be considered probably toxic in humans, based on sufficient evidence of chronic toxicity in animals.

TDCP exposure also induced tumors at multiple doses in the kidneys and liver of both male and female rats. Therefore, TDCP may be considered a probable human carcinogen based on sufficient evidence in animals (Ferrante 1999b; Bittner et al. 2001). This conclusion is further supported by structural similarity to another animal carcinogen, TRIS. TDCP and its metabolites were genotoxic in some assays, although the majority of tests were negative.

Based on the available data, the CPSC staff concludes that there is inadequate evidence of reproductive toxicity and or developmental toxicity in animals (CPSC 1992). In addition, there is inadequate evidence of neurotoxicity in animals.

B. Aromatic Phosphate Plasticizers (APP's)

The toxicity of various aromatic phosphate plasticizers (APP's) has been reviewed by the CPSC staff (Bittner 2001; Bittner et al. 2001; Ferrante 1999a) and others (EPA 2005a; IPCS 1990, 1991; NRC 2000). The toxicity of the APP's varies among individual compounds and commercial mixtures. Much of the available toxicity data are for commercial mixtures containing two or more APP's. The toxicity data for the APP's are summarized below.

In general, the acute toxicity of APP's is low, with oral LD_{50} values in rats ranging from 3,000 mg/kg to >20,000 mg/kg (Ferrante 1999a). Tricresyl phosphate (TCP) (mixture of isomers) (1330-78-5) and *o*-tricresyl phosphate (*o*-TCP) (78-30-8) are the most toxic with regard to acute toxicity. APP's are weakly irritating or non-irritating in the skin and eyes of rats or rabbits. The APP's were generally non-genotoxic in *Salmonella* and in mammalian systems.

1. Toxicokinetics

TCP (mixed isomers) (NTP 1994) and *o*-TCP (Somkuti and Abou-Donia 1990) were readily absorbed following oral exposure in rats. The highest levels of radiolabel were found in adipose tissue, muscle, erythrocytes, and liver in rats given [^{14}C]-*o*-TCP (Somkuti and Abou-Donia 1990). However, the highest level of the neurotoxic metabolite, saligenin cyclic *o*-tolyl phosphate, was found in the testes. Percutaneous absorption of *o*-TCP in cats was biphasic. Initially, 73% of *o*-TCP applied to skin was absorbed in 12 hours, while the remainder was absorbed at a constant rate of 0.34 d^{-1} (Nomeir and Abou-Donia, 1984). Initially, unmetabolized *o*-TCP was found primarily in the brain, spinal cord, and sciatic nerve in cats. Metabolites were found primarily in the liver, lung, and kidney. In contrast to TCP, 2-ethyhexyldiphenyl

* 16 CFR 1500.3 (c)(1).

phosphate (EHDP) was reported to be poorly absorbed from the intestinal tract in humans and Wistar rats (reviewed in Ferrante 1999a; IPCS 1990).

o-TCP is metabolized by three pathways (Abou-Donia et al. 1990; Casida et al. 1961; Eto et al 1962; IPCS 1990; Nomeir and Abou-Donia 1984, 1986; Somkuti and Abou-Donia 1990). First, one or more methyl groups are hydroxylated by mixed function oxidase. The resulting hydroxylated compound then undergoes a cyclization reaction to form saligenin cyclic *o*-tolyl phosphate, and releasing o-cresol (Figure 3). Second, *o*-TCP is hydrolyzed to the diester, monoester, and inorganic phosphate, which also releases *o*-cresol. Third, hydroxymethyl groups may be further oxidized to the aldehyde and carboxylic acid. The meta and para isomers of TCP are also hydroxylated (Kurebayashi et al. 1985; Johnson 1975). In rats, *o*-TCP metabolites are excreted mainly in urine, while the meta isomer metabolites are mainly excreted in feces, and the para isomer divided between urine and feces (Kurebayashi et al. 1985; NTP 1994). TPP was hydrolyzed to the diester by mixed function oxidase and aryl esterase in rat liver microsomes (Sasaki et al. 1984).

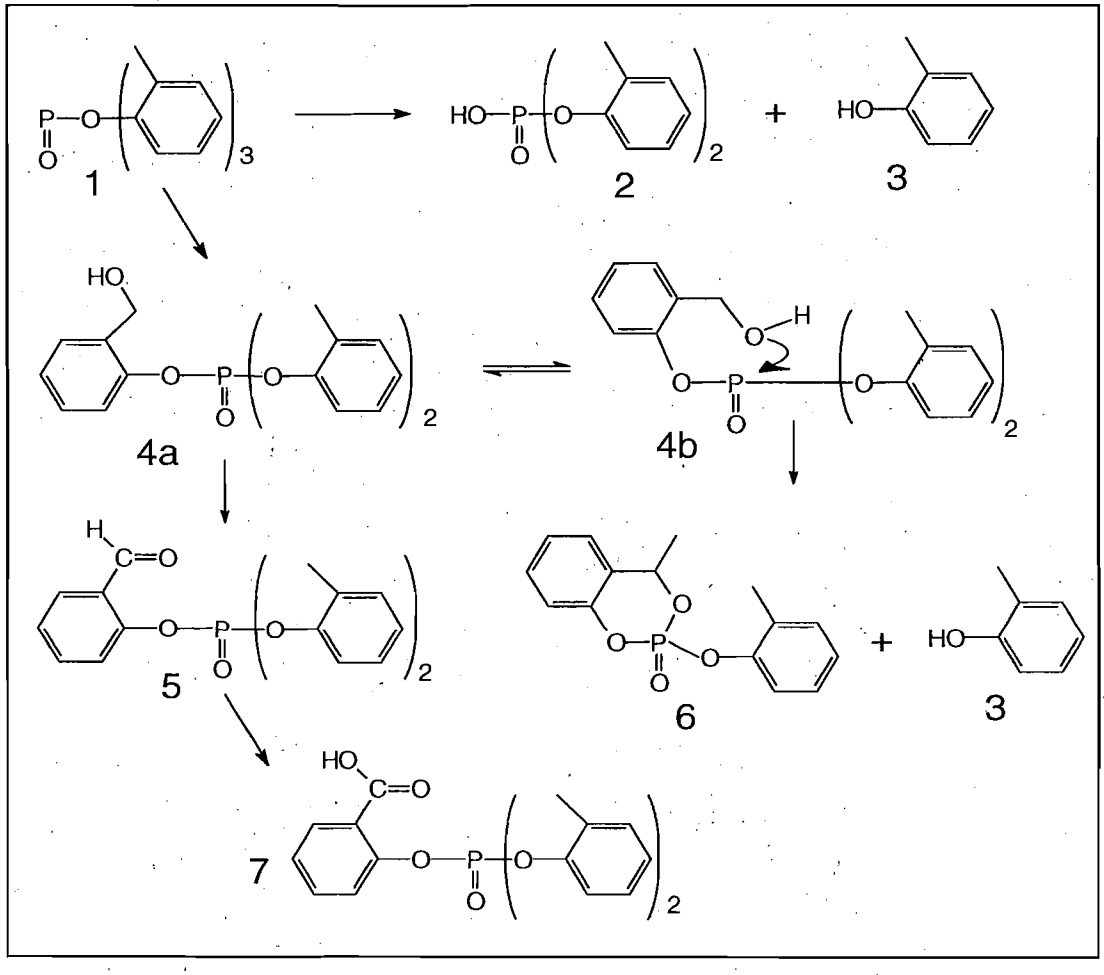

Figure 3. Metabolism of *o*-tricresyl phosphate. Structures: 1) tricresyl phosphate (TCP); 2) dicresyl phosphate; 3) cresol; 4a,b) hydroxymethyl intermediate; 5) aldehyde; 6) saligenin cyclic *o*-tolyl phosphate; 7) carboxylic acid. Adapted from Somkuti and Abou-Donia (1990).

2. Subchronic and Chronic Studies

TCP was tested in two-year gavage bioassays in $B6C3F_1$ mice and F-344 rats (NTP 1994). There was "no evidence of carcinogenic activity" in mice or rats. Non-neoplastic effects were found in female rats at 300 ppm (15 mg/kg-d), including cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cells hyperplasia. The NOAEL was 150 ppm (7 mg/kg-d) in female rats. The incidences of clear cell foci, fatty change, and ceroid pigmentation of the liver were significantly increased in male mice at 125 or 250 ppm (13 or 27 mg/kg-d). In addition, increased incidence and severity of ceroid pigmentation of the adrenal cortex occurred in female mice at 250 ppm (37 mg/kg-d). The NOAEL was 60 ppm (7 mg/kg-d) in male mice.

SD rats exposed to EHDP in feed for 90 days had enlarged livers and adrenal glands (Solutia 1998). Histopathological effects were observed in the adrenal cortex in both sexes and ovarian hyperplasia in females. The overall LOAEL was 0.2% (about 164 mg/kg-d). A NOAEL was not established. EHDP was also tested in a two-year bioassay in Carworth albino rats (Treon et al. 1953). Rats were given 0, 0.0625, 0.125, or 1.0% EHDP in feed. There was no evidence of carcinogenicity, but there was a decreased growth rate at 1% in feed. No significant increases in gross or microscopic histopathological effects were found. No effects in the adrenal cortex or ovaries were reported. However, the histopathological methods and the organs examined were not described in detail. The NOAEL was 0.125% or approximately 100 mg/kg-d (Ferrante 1999a)..

3. Reproductive and Developmental Toxicity

Oral TCP exposure led to infertility and reduced fertility in mice (Chapin et al. 1988; NTP 1985) and rats (Carlton et al. 1987). The fertility of both male and female mice was affected (NTP 1994). Reduced sperm concentration and motility, as well as increased incidence of abnormal morphology, was reported in rats (Carlton et al. 1987) and mice (Chapin et al. 1988; NTP 1985). Histopathological effects in the testes, epididymes, and ovaries were also observed (Carlton et al. 1987). The LOAEL for reproductive effects was 62.5 mg/kg-d (the lowest dose tested) in a continuous breeding study in male CD-1 mice (Chapin et al. 1988; NTP 1985).

Oral exposure to *o*-TCP lead to effects on sperm motility and morphology, as well as testicular effects, in F-344 rats (Somkuti et al. 1987a,b, 1991). The authors considered 25 mg/kg-d as the NOAEL and 10 mg/kg-d as the NOAEL. The teratogenicity of *o*-TCP was tested in Long Evans rats at doses of 0, 87.5, 175, and 350 mg/kg-d (Tocco et al. 1987). Dams were treated on GD's 6 through 18. The high dose was lethal to the dams. Malformations and variations at the low- and mid-doses were not significantly different from the controls. Mele and Jensh (1977) gave doses of 0, 500, or 750 mg/kg-d *o*-TCP to pregnant Wistar rats on GD's 18 and 19. The authors reported that there were no malformations or skeletal variations. No other details are available.

A mixture of two commercial products containing EHDP was tested in a one-generation study in SD rats (Monsanto 1993; Robinson et al. 1986). Groups of 16 male and 32 female rats were fed 0, 0.2%, 0.4%, or 0.8% DEHP. Males received EHDP continuously from 70 days prior to mating through the end of the study, while females received EHDP from 21 days prior to mating through the end of the study. Initially, treatment-related reductions in food and water

consumption were observed in mid- and high-dose males and high dose females. This was attributed to the unpalatability of EHDP. Reduced food and water consumption persisted in high-dose females throughout the study.

There were no adverse effects on fertility in either sex. Liver weights were increased in a dose-dependent manner in parental (F_0) males and females. Relative increases in adrenal, caecal, and kidney weights were observed in high-dose males and females. In addition, spleen weights were reduced in mid- and high-dose females, while hypertrophy and luteinization of ovarian stromal cells occurred at the high dose. Centrilobular and periportal hypertrophy was found in the liver in high-dose males and females.

Body weight gain was significantly reduced in mid- and high-dose pups (F_1). Pup survival was reduced at the high dose. The authors attributed these effects to the nutritional status of the dams. In mid- and high-dose pups, liver and adrenal weights were significantly increased, while spleen weights were reduced. The reproductive NOAEL considered to be 0.2% EHDP, or roughly 144 mg/kg-d.

In a teratology screening study, female CD rats were given 0, 300, 1000, or 3000 mg/kg-d Santicizer™ 141 (>90% EHDP) orally on GD's 6 through 15 (Robinson et al. 1986; Solutia 1998). Maternal effects included increased hair loss and yellow staining or matting in the mid- and high-dose groups. Maternal weight was reduced at the high dose, and some animals had inguinal fissures. The incidences of skeletal variations were increased at all doses. Malformations—such as eye anomalies, scoliosis, and dwarfism—were found at the mid- and high doses. The authors considered the incidences of variations and malformations to be not treatment-related, because they were within the range of historical controls.

In developmental assays in rats, reported fetal effects included increased frequency soft tissue variations with TPP (see below) (Welsch et al. 1987).

4. Neurotoxicity

The APP's are known primarily for their neurotoxicity. An estimated 50,000 cases of accidental ingestion of *o*-TCP occurred in the 1930's in the southern U.S. when "Ginger Jake," an alcoholic extract of Jamaican ginger popular during prohibition, was adulterated with *o*-TCP" (reviewed in Ferrante 1999a; IPCS 1990; Weiner and Jortner 1999). Ingestion of mixtures containing *o*-TCP have resulted in neuropathy, paralysis, axonal degeneration, and/or death. Most patients recovered over a period of up to two years, although some remained permanently paralyzed. Other ingestions have occurred in an occupational setting. Sensitivity among humans is quite variable. Paralysis may occur with doses as low as 2 mg/kg, and 1,000 mg/kg may be fatal (Ferrante 1999a).

APP's induce a delayed neurotoxicity in animals and humans characterized by ataxia, flaccid paralysis, axonal degeneration, and demyelination, referred to as organophosphate-induced delayed neurotoxicity (OPIDN) (reviewed in Weiner and Jortner 1999). The syndrome associated with the APP's is distinct from the effects associated with anticholinergic nerve agents. Humans and other primates, canines, felines, ruminants, and hens are sensitive to

OPIDN, while laboratory rodents are less sensitive. Hens are considered the best animal model for OPIDN in humans, and have been used extensively in laboratory studies (e.g., Johannsen et al. 1977; Johnson 1975; Weiner and Jortner 1999). The domestic hen is susceptible, exhibits clearly detectable clinical signs, and the time course for developing neuropathy is similar to that in humans (Weiner and Jortner 1999). *o*-TCP is the most neurotoxic APP in animals and is a known neurotoxicant in humans (Ferrante 1999a; NRC 2000). APP's inhibit a variety of esterases, including plasma pseudocholinesterase, erythrocyte cholinesterase, non-specific carboxylesterase, acetylcholinesterase, and neurotoxic esterase (NTE). The severity of OPIDN symptoms generally correlate with the inhibition of NTE, which is a smooth endoplasmic reticulum-bound carboxylesterase found especially in nervous tissue (e.g., Dollahite and Pierce 1969; Johnson 1974; NTP 1994; Weiner and Jortner 1999). Neurotoxicity appears to require irreversible inhibition of NTE, through the formation of a stable, covalently-bound intermediate (Johnson 1974, 1975). Non-toxic APP's are reversible NTE inhibitors, and may protect against neurotoxic APP's.

Extensive studies of structure activity relationships have been performed (Johannsen et al. 1977; Johnson 1975). APP's having one or more alkyl groups at the *ortho* position are neurotoxic, provided that there is at least one hydrogen at the α-alkyl position to allow formation of the cyclic metabolite. Thus, the *t*-butyl group is inactive. Neurotoxicity is greater in isomers having only one *ortho* substituent. Increasing chain size and branching of the *ortho* substituent tends to reduce neurotoxicity. *Para*-substituted APP's are neurotoxic provided that there are at least two α-hydrogens. *Meta*-substituted and unsubstituted APP's (i.e., TPP) are not neurotoxic. Thus, the relative toxicity of the APP's is as follows: TPP < butylphenyl phosphate < isopropylphenyl phosphate < trixylenyl phosphate < TCP < *o*-TCP (Weiner and Jortner 1999). Using a multiple dose regimen, the dose causing a 50% incidence of neurotoxicity in hens (ED_{50}) was estimated to be 420 mg/kg for *o*-TCP and 10,000 mg/kg for isopropylphenyl diphenyl phosphate (IPDP) (Johannsen et al. 1977).

5. Toxicity under the FHSA

Previously, the CPSC staff concluded that *o*-TCP is known to be neurotoxic in humans (Bittner 2001; Ferrante 1999a). The staff also concluded that TCP (mixed isomers) is probably toxic, based on sufficient evidence of neurotoxicity, chronic organ toxicity, and reproductive toxicity in animals; 2-ethylhexyl diphenylphosphate (EHDP) is probably toxic, based on sufficient evidence of chronic organ toxicity in animals; and isodecyl diphenylphosphate (IDDP) is possibly toxic, based on limited evidence of chronic organ toxicity in animals (Table 2). TPP and PIP are discussed below.

C. Triphenyl Phosphate (TPP)

The toxicity data for TPP have been reviewed by the CPSC staff (Bittner et al. 2001; Ferrante 1999b) and others (EPA 2005a; IPCS 1991). The range of studies on TPP was limited. Oral LD_{50} values were reported to range from 1,320 mg/kg to >5,000 in mice; 3,000 mg/kg in rabbits; and from 3,000 mg/kg to >20,000 mg/kg in rats (reviewed in Ferrante 1999a; IPCS 1991). A 70% solution of TPP in alcohol was not irritating to mouse skin (Sutton et al. 1960). No other

data on skin or eye irritation were reported, although other APP's were either non-irritating or weakly irritating to rabbit skin and eyes.

Several cases of contact dermatitis from products containing TPP or related compounds have been reported (Camarasa and Serra-Baldrich 1992; Carlsen et al. 1986; Hjorth 1964; Holden et al. 2006). TPP is used as a plasticizer in plastics and cellulose acetate. The products involved included eyeglass frames, an oxygen mask, an adhesive, and cellulose acetate. Patients reacted to TPP in patch testing, at levels from 0.05% to 0.5% in petrolatum. Thus, TPP is capable of eliciting an allergic response in humans by dermal exposure. Cross-reactivity with other triaryl phosphates and triaryl phosphites is likely to occur.

1. Genotoxicity

TPP was not mutagenic in *Salmonella* (TA 1535, TA 1537, TA 1538, TA 98, and TA 100), *Saccharomyces cerevisiae* (D4 strain), or L5178Y mouse lymphoma cells (thymidine kinase locus) (reviewed in Ferrante 1999a; IPCS 1991). Studies were done both with and without metabolic activation.

2. Toxicokinetics

No data are available on the metabolism of TPP in animals or humans. TPP was reported to be hydrolyzed to the diester by rat liver microsomes (Sasaki et al. 1984). Because TPP lacks alkyl substituents, it cannot be oxidized to the neurotoxic metabolite, as occurs with other APP's (Johannsen et al. 1977; Johnson 1975).

The percutaneous absorption of formulations containing TPP through human epidermis was reported (Scott and Thompson 1985). Neat Reofos™ 50 or Reolube™ 46 were applied as an "infinite dose" to the epidermal side of cadaver epidermis placed on a static diffusion cell. The receptor fluid was 70% ethanol. The authors calculated a diffusion constant of 1.6×10^{-6} cm/h for TPP. However, the experimental design was unusual in that the other components of the formulation were not identified and the receptor fluid was essentially non-aqueous. The use of a static cell could lead to an underestimate of absorption. Therefore, the usefulness of this study for estimating human risk was considered questionable (EPA 1985).

3. Subchronic and Chronic Studies

TPP has been subjected to several repeated-dose oral studies in animals. However, no subchronic or chronic studies with full pathology have been reported. In one study, groups of 5 male Holtzman rats were exposed to 0, 0.01%, or 0.5% TPP in feed for 35 days (Sutton et al. 1960). Relative liver weights were significantly elevated at 0.5% TPP; absolute organ weights were not reported. Body weights of exposed animals were slightly reduced, but this effects was reversible during the two-week recovery period. Hematology tests were normal and no gross abnormalities observed. Detailed histopathology results were not provided.

In a study of neuromotor function, groups of 10 male SD rats were given 0, 0.25%, 0.5%, 0.75%, or 1% TPP in feed for 4 months (Sobotka et al 1986). The resulting dose levels were 0, 161,

345, 517, and 711 mg/kg-d. Behavioral tests were performed monthly. No significant effects on behavior were observed. There was a significant, dose-dependent reduction in weight gain. The NOAEL for reduced weight gain was 0.25% (161 mg/kg-d).

In an immunotoxicity study from the same laboratory, groups of 10 male and 10 female SD rats were given TPP at 0, 0.25%, 0.5%, 0.75%, or 1% in feed for 4 months (Hinton et al. 1987). At 60 days, 3 rats from each sex/dose group were sacrificed. Beginning at 60 days, 5 rats from each dose/sex group were immunized with sheep red blood cells. Immunized and non-immunized TPP-exposed males generally gained weight at a reduced rate, but the differences were statistically significant only for some combinations of dose and time. TPP-exposed animals generally consumed slightly more food than controls. Body weights and food consumption were generally similar in immunized and non-immunized animals. Relative weights of the thymus and spleen were generally unaffected by TTP exposure or immunization. No significant effects on thymus and spleen histopathology or antibody titers were observed. There was a small, non-significant increase in total serum protein in TPP-exposed animals.

TPP gave negative results in the strain A mouse assay for pulmonary carcinogens (Theiss et al. 1977). Groups of 20 male strain A mice were given up to 18 intraperitoneal injections of 0, 20, 40, or 80 mg/kg TPP. All mice were sacrificed at 24 weeks following the first injection. TPP did not significantly increase the incidence of pulmonary adenoma in treated mice.

Workers exposed to a weighted average concentration of 3.5 mg/m^3 TPP (range 1.8 to 12 mg/m^3 for different operations) showed no neurological symptoms, dermatitis or other unusual symptoms (Sutton et al. 1960). Erythrocyte esterase activity was significantly reduced (8% lower than controls), but plasma esterase activity was not affected. The duration of exposure was not reported. Potential dermal and oral exposures were not assessed.

4. Reproductive and Developmental Toxicity

One study of the potential reproductive and developmental effects of TPP has been reported. Groups of 40 male and 40 female SD rats were fed TPP at levels of 0, 0.25%, 0.5%, 0.75%, or 1% for 91 days prior to breeding (Welsh et al. 1987). The resulting dose levels were 0, 166, 341, 516, and 690 mg/kg-d. The dams were sacrificed on GD 20. Dams exposed to TPP consumed more feed than controls. There was a dose-dependent decrease in dam body weights, although it was statistically significant only at the high dose. No effects on reproduction were observed.

TPP-exposed male pups weighed significantly more than controls at 0.5% and 1%. The incidences of hydroureter and enlarged ureters (both moderate to severe) were significantly increased in all TPP-exposed groups, although there was no clear dose-response. The number of fetuses with two or more soft tissue variations was significantly elevated in all TPP-exposed groups, except the high dose, which was non-significantly elevated. The number of litters with fetuses having at least two soft tissue variations was significantly elevated at 0.5% and 1%. A clear dose response was not observed for any of the reported effects. The numbers of fetuses or litters with one or more soft tissue variations were not significantly elevated. The authors concluded that there was evidence of maternal toxicity at the high dose (decreased weight gain), and that the observed increases in soft tissue variations were not dose-dependent. The CPSC

staff concludes that it is uncertain whether the increased in soft tissue variations is biologically significant.

5. Neurotoxicity

In an early study, TPP was reported to cause delayed paralysis with demyelination in cats and monkeys, but not chickens or rabbits (Smith et al. 1932). Subsequently, practical grade TPP was reported to cause a delayed paralysis suggestive of OPIDN in cats at 200 to 400 mg/kg (Sutton et al. 1960). No effects were found in rats, mice, or guinea pigs. However, in studies with purified, synthetic TPP, no evidence of neurotoxicity or neuropathology was observed in cats given from 400 mg/kg to 1,000 mg/kg TPP subcutaneously (Wills et al. 1979). Other toxic effects—anorexia, weight loss, and generalized vascular damage, perivascular edema, and fatty changes in the liver—were observed at all doses, except controls. The authors suggested that the earlier study (Smith et al. 1932) used TPP derived from coal tar, and probably contained neurotoxic impurities.

TPP caused a dose-dependent inhibition of whole blood cholinesterase in mice exposed either orally or intraperitoneally at doses from 10 to 500 mg/kg-d (Sutton et al. 1960). No evidence of neurotoxicity was observed. In mice exposed by inhalation (757 mg/m^3 TPP for up to 4 hours or 363 mg/m^3 for 6 hours), there was a small, non-significant decrease in whole blood cholinesterase activity. TPP inhibited human plasma and erythrocyte cholinesterase activity *in vitro*.

TPP did not induce delayed neurotoxicity (OPIDN) in numerous studies in hens (reviewed in Johannsen et al. 1977; Johnson 1975; Weiner and Jortner 1999). TPP cannot be metabolized to a neurotoxic intermediate due to the absence of alkyl substituents.

No neuromotor effects were observed in SD rats fed TPP for 4 months at doses up to 711 mg/kg-d (Sobotka et al. 1986) (see above). Measures of neuromotor function included motility, exploratory behavior, balance, coordinated motor activity, and grip strength.

TPP inhibited the development of neurite-like outgrowths in mouse neuroblastoma and rat glioma cells *in vitro* (Henschler et al. 1992). With TPP, 50% inhibition was observed at concentrations (IC_{50}'s) from $1.5x10^{-5}$ to $7.7x10^{-5}$ M. TPP was roughly as effective as *o*-TCP, which had IC_{50} values from $3.1x10^{-5}$ to $3.8x10^{-5}$ M. The authors concluded that TPP may have "very slight" neurotoxic potential.

No neurological symptoms were observed in workers exposed to a weighted average concentration of 3.5 mg/m^3 TPP (range 1.8 to 12 mg/m^3 for different operations) (Sutton et al. 1960) (see above). Erythrocyte esterase activity was significantly reduced (8% lower than controls), but plasma esterase activity was not affected.

Several cases of accidental ingestions or occupational exposures to TPP have been reported (reviewed in Ferrante 1999a; IPCS 1991). However, all of these were mixtures containing other neurotoxic compounds. Therefore, the significance of these reports is unknown.

6. Other Studies

Micromolar levels of TPP and some isopropylated triphosphates activated (or derepressed) human constitutively active receptor (CAR) and pregnane X receptor (PXR) *in vitro* (Honkakoski et al. 2004). Variable results were obtained with mouse receptors. CAR and PXR are ligand activated transcription factors that are part of the superfamily of nuclear receptors. CAR and PXR induce genes that are involved in steroid metabolism, as well as numerous other unidentified genes.

7. Toxicity under the FHSA

The database for TPP toxicity is limited. No chronic studies of any kind and no subchronic studies with complete histopathology have been reported. The range of reported LD_{50} values is broad. Reported LD_{50} values in rats ranged from 3,000 mg/kg to >20,000 mg/kd (reviewed in Ferrante 1999a; IPCS 1991). While some LD_{50} values were below 5,000 mg/kg, the majority were greater than 5,000 mg/kg. The lower (more toxic) values could be due to the presence of impurities in some preparations. Considering all of the data, the CPSC staff concludes that there is limited evidence of acute toxicity in animals. Therefore, TPP is not considered acutely toxic, as defined by the FHSA.*

In addition, the staff concludes that there is limited evidence of chronic toxicity in animals, based on decreased body weight gain in a 90-day neurotoxicity study in male rats (Sobotka et al. 1986). Additional data are needed to assess the chronic toxicity of TPP. The staff further concludes that there is inadequate evidence of developmental toxicity in animals, based on increased incidence of soft tissue variations in one study (Welsh et al. 1987). In the same study, there was inadequate evidence of reproductive effects. Finally, the staff concludes that there is, at most, limited evidence of neurotoxicity in animals. TPP was neurotoxic in some studies in cats, although it was not neurotoxic in hens or mice (reviewed in Johannsen et al. 1977; Johnson 1975; Weiner and Jortner 1999). The positive studies may have been due to the presence of impurities. Alternatively, TPP may simply be a very weak neurotoxicant. Thus, there is inadequate evidence of neurotoxicity in animals.

Overall, TPP may be considered "possibly toxic in humans" based on limited evidence of toxicity in animals, that is, reduced weight gain in a 90-day feeding study (Sobotka et al. 1986; reviewed in Bittner et al. 2001; Ferrante 1999a). The finding that TPP is "possibly" toxic is not sufficient to satisfy the regulatory definition of "toxic" (CPSC 1992). However, this conclusion is based on limited data. It does not mean that TPP is not toxic. Rather, it means that additional information is needed to assess its toxicity and derive an ADI.

* 16 CFR 1500.3 (c)(1).

D. Phenol Isopropylated Phosphate (PIP)

The toxicity of PIP has been reviewed by the CPSC staff (Bittner et al. 2001; Ferrante 1999a) and others (EPA 2005a; Henrich 2001). Briefly, PIP is typically a complex mixture of PIP isomers and TPP, and may be blended with other aromatic phosphates. PIP is generally prepared by alkylation of phenol prior to reaction with phosphorus oxychloride ($POCl_3$). Commercial products differ in their degree of alkylation, which determines the viscosity of the mixture. PIP is sold under a variety of trade names, including Kronitex™, and Durad™, OS-70™, and Reofos™. Various commercial products and isomers have been assigned different Chemical Abstracts Service numbers.* The toxicity of PIP, including various commercial products and specific isomers, is summarized below.

1. Acute Toxicity

PIP and formulations containing PIP are not acutely toxic (reviewed in EPA 2005a; Ferrante 1999a; Henrich 2001). The oral LD_{50} in various strains of rat is greater than 5,000 mg/kg (FMC 1969; FMC 1979; Freeman 1990; Stauffer 1979). The minimum lethal oral dose of OS-70™ was from 3.2-to-4.7 mL/kg in rats (Ferrante 1999a). Observations included respiratory distress and CNS effecrts. Rabbits dying after oral or dermal exposure to OS-70™ had degenerative liver and kidney changes, and acute hyperemia in the viscera (Ferrante 1999a).

The dermal LD_{50} was >2,000 mg/kg in SD rats (Freeman 1990; Henrich 2001). The minimum lethal dose of Durad-110™ was from 1.6-to-2.5 mL/kg by the dermal route (Ferrante 1998a). The 1-hour inhalation LC_{50} was > 200 mg/L in SD rats (Ferrante 1999a; Freeman 1990; Henrich 2001).

The oral LD_{50}'s of Kronitex™ K-50, K-100, K-200, K-200B, and K-300 in albino Wistar rats were all >20,000 mg/kg (FMC 1979). Clinical signs of toxicity generally included visceral hemorrhage and hematuria. These products are PIP formulations with increasing degrees of isopropylation. No mortalities occurred in rats administered up to 40,000 mg/kg of K-300. However, clinical signs of toxicity included alternating hypoactivity and hyperactivity, increased salivation, piloerection, diarrhea, excessive urination, and wet, oily coat. The dermal LD_{50} values of these compounds in rabbits were all >10,000 mg/kg. Their inhalation LC_{50}'s in rats were all less than 200 mg/L.

2. Dermal and Ocular Effects

PIP was non-irritating to moderately irritating to rabbit skin and either non-irritating or slightly irritating in the rabbit eye (FMC 1979; Ferrante 1999a; Freeman 1990; Henrich 2001; Stauffer 1979). Kronitex™ K-100 was mildly irritating to skin and non-irritating to eye in rabbits (FMC 1976). K-50, K-200, and K-300 were non-irritating to both the skin and eye in rabbits.

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* 68937-41-7, 28108-99-8, 64532-94-1, 93925-53-2, 28109-00-4, 69500-29-4, 96300-97-9, 74315-11-0, 26967-76-0, 64532-95-2, 69515-46-4, and 68155-51-1.

3. Genotoxicity

PIP was not mutagenic in *Salmonella* tester strains TA98, TA100, TA1535, TA1537, and TA1538, either with or without metabolic activation (reviewed in EPA, 2005, Ferrante 1999a; FMC 1979; Henrich 2001; Stauffer 1979). Kronitex™ 110 was mutagenic without metabolic activation in TA1535 and TA1537, but not in strains TA98, TA100, or TA1538 (Microbiological Associates 1978). Interestingly, Kronitex™ 110 was not mutagenic with metabolic activation in either TA98, TA100, TA1535, TA1537, or TA 1538. However, in another study, Kronitex™ K-110, K-100B, and K-200 were not mutagenic in the same strains, with or without activation. *o*-IPDP was reported to be non-mutagenic in *Salmonella* (Stauffer 1979).

PIP failed to induce unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro*. It was unable to induce phenotypic transformation of Balb/c 3T3 cells *in vitro* (EPA 2005a; FMC 1981). However, *o*-isopropylphenyl diphenyl phosphate was able to transform Balb/c cells, and was weakly mutagenic with metabolic activation in mouse lymphoma cells (Stauffer 1979). In addition, PIP induced sister chromatid exchange in the bone marrow cells of Chinese hamsters following two oral doses, but not following a single dose.

4. Toxicokinetics

No data were available on the metabolism of PIP. However, other aromatic phosphates are hydrolyzed to the diester (see above). In addition, alkyl substituted APP's are oxidized at the 2-alkyl position. The resulting hydroxylated compound may then form a cyclic intermediate that is neurotoxic.

The percutaneous absorption of formulations containing IPDP through human epidermis was reported (Scott and Thompson 1985). Neat Reofos™ 50 or Reolube™ 46 were applied as an "infinite dose" to the epidermal side of cadaver epidermis placed on a static diffusion cell. The receptor fluid was 70% ethanol. The authors calculated a diffusion constant of 2.2×10^{-5} cm/h for IPDP. However, the experimental design was unusual in that the other components of the formulation were not identified and the receptor fluid was essentially non-aqueous. The use of a static cell could lead to an underestimate of absorption. Therefore, the usefulness of this study for estimating human risk was considered questionable (EPA 1985).

5. Subchronic and Chronic Studies

Limited data are available on the subchronic toxicity of PIP in mammals. No chronic studies have been reported. Groups of 10 male and 10 female SD rats were given 0, 0.1, 0.5 or 1% PIP (Kronitex™ 100) in the diet for 28 days (FMC 1977). These doses correspond to 0, 350, 1600, and 3000 mg/kg-d in males and 0, 380, 1500, and 3400 mg/kg-d in females. There were 4 deaths each at the low- and mid-dose, and 3 deaths at the high dose, as compared to 1 death in the controls. The incidence of deaths is not significantly different from the controls by a Fisher's exact test. Relative liver weights were increased at all doses. There were clinical chemistry effects at the mid and high dose, and hematological effects at the high dose. There were no gross lesions and no abnormal histopathology in the liver or kidney. Other organs were not examined microscopically. No other details were provided.

Increased white blood cell and lymphocyte counts were observed in workers exposed to K-50™ (Kolodner et al. 1987). Erythrocyte cholinesterase was not affected, and no neurological symptoms were reported. White blood cell and lymphocyte counts were elevated at all doses. There was no reduction in erythrocyte cholinesterase and there were no neurological effects. No other details were reported.

6. Reproductive and Developmental Toxicity

In a reproductive and developmental screen, male and female rats were administered PIP by gavage for 40 days at doses of 0, 25, 100, or 400 mg/kg-d (reviewed in EPA 2005a). The liver and adrenal glands were affected in adult males and females; females were more sensitive. The LOAEL for organ toxicity was 25 mg/kg-d. There was reduced fertility at the mid- and high dose, and reduced pup survival at the high dose. In addition, ovarian weights were affected at all doses, and epididymal weights at the mid and high dose. No other details were reported. See above (Subchronic and Chronic Studies).

7. Neurotoxicity

Numerous studies on the neurotoxicity of PIP in hens have been reported (reviewed in EPA 2005a; Ferrante 1999a; FMC 1977, 1979; Henrich 2001; Johannsen et al. 1977). PIP and related isomers are capable of causing OPIDN in hens at relatively high doses. Phosphoflex™ 41P was neurotoxic in hens at 4,000 mg/kg (FMC 1977). The ED_{50} for Kronitex™ 200 was reported to be greater than 20,000 mg/kg (Cascieri and Poinsett 1977; Ross et al. 1979). The ED_{50} for *o*-IPDP was 10,000 mg/kg, as compared to 420 mg/kg for *o*-TCP (Johannsen et al. 1977).

In a series of studies, the acute ED_{50} in hens was estimated as: >4,000 mg/kg for Kronitex™ K-50; ~8,000 mg/kg for K-100; >20,000 mg/kg for K-200; and >16,000 mg/kg for K-300 (FMC 1977). In these studies, 400 mg/kg *o*-TCP caused paralysis in at least 90% of hens.

8. Other effects

Kronitex™ 50 was reported to inhibit monocyte phagocytosis and IgG synthesis in human cells *in vitro*, while stimulating the release of leukotrienes and prostaglandins (Newcombe and Warr 1985). A tris(isopropylated) phenyl phosphate was reported to reduce Fc receptor activity and chemotaxis *in vitro*, with guinea pig alveolar macrophages (BIBRA 1987). These studies suggest possible effects of PIP on the immune system and inflammation.

9. Toxicity under the FHSA

The CPSC staff concludes that there is limited evidence of neurotoxicity in animals. Although PIP is neurotoxic in hens at high doses, it is very weak in comparison to other APP's. There are no reports of neurotoxicity in humans or other mammals. There is also limited evidence of chronic organ effects in animals, including two poorly documented studies in rats, and inadequate evidence of reproductive/developmental effects in animals. Therefore, the CPSC

staff concludes that PIP is possibly toxic in humans, based on limited evidence of toxicity in animals (neurotoxicity and chronic organ toxicity).

E. Octyl Tetrabromobenzoate (OTB)

Limited toxicity data for octyl tetrabromobenzoate (OTB) are available (reviewed in EPA 2005a). SD rats were given single oral doses of either OTB isomer. There were no deaths, although exposed animals exhibited effects including piloerection and hunched posture. Thus, both isomers have oral LD_{50} values >2000 mg/kg in rats. No other animal or human toxicity data or empirical physico-chemical properties are available.

There is insufficient information to determine whether OTB is "toxic" under the FHSA. The only conclusion that may be made is that OTB is not "highly toxic" with regard to acute toxicity. In addition, no toxicity data on structural analogues were identified in National Library of Medicine databases.

F. Melamine

The toxicity of melamine (1,3,5-triazine-2,4,6-triamine) was reviewed by the CPSC staff (Thomas and Brundage 2004) and IARC (IARC 1986, 1999). Briefly, the oral LD_{50} was between 3,200 and 3,800 mg/kg in F344 rats (NTP 1983). Symptoms included lacrimation, dyspnea, intermittent tremors, paralysis, and coma. A single dose of 2,400 mg/kg melamine in rats lead to crystalluria (dimelamine monophosphate) and diuresis (Lefaux 1968).

A 1% aqueous solution caused little or no irritation and did not induce sensitization on occluded guinea pig skin (Trochimowicz et al. 1994). Melamine was not irritating to rabbit skin at doses up to 1,000 mg/kg for 18 hours. A 10% aqueous solution was not irritating to the eyes of rabbits, although the dry solid caused mild, reversible irritation.

1. Genotoxicity

Melamine was not mutagenic in *Salmonella* with or without metabolic activation (Haworth et al. 1983; NTP 1983). It did not induce sister chromatid exchange (SCE) in Chinese hamster ovary cells *in vitro* or micronuclei in mouse bone marrow *in vivo* (Mast et al. 1982a,b). Melamine failed to initiate papilloma formation in an initiation-promotion assay in mouse skin (Perrella and Boutwell, 1983).

2. Toxicokinetics

In rats given a single oral dose of ^{14}C-melamine, radiolabel was found primarily in the kidney and bladder (Mast et al. 1983). Ninety percent was excreted in the urine, as unmetabolized melamine, within 24 hours. Negligible amounts of radiolabel were found in exhaled air or feces.

3. Suchronic and Chronic Studies

F344 rats and B6C3F1 mice were given melamine in the diet at levels up to 1.8% for 13 weeks (Melnick et al. 1984). These doses were equivalent to 1700 mg/kg-d in male rats; 1600 mg/kg-d in female rats; 4700 mg/kg-d in male mice; and 5900 mg/kg-d in female mice. Uroliths (bladder stones) were found in treated animals, especially males. Ulceration of the bladder epithelium was observed in treated male and female mice, but this was statistically independent of urolith formation. Increased incidence of epithelial hyperplasia was found in treated male rats.

In a two-year dietary study, male F344 rats and B6C3F1 mice were given 0, 0.225, or 0.45% melamine, and females were given 0, 0.45, or 0.9% melamine (Melnick et al. 1984; NTP, 1983). This resulted in doses of 0, 125, and 270 mg/kg-d in males rats and 0, 252, and 566 mg/kg-d in female rats. The doses in mice were 0, 327, and 688 mg/kg-d in males and 0, 367, and 964 mg/kg-d in females. The incidence of transitional-cell carcinomas of the urinary bladder was significantly elevated in high-dose male rats. In addition, there was a statistically significant association between the presence of bladder carcinoma and uroliths. In female rats, the incidence of chronic kidney inflammation was elevated at both the low and high dose. The incidence of chronic inflammation and epithelial hyperplasia of the urinary bladder and increased incidence of uroliths were elevated in dosed male mice. No tumors were found in male or female mice.

In another study, male F344/DuCrj rats were fed melamine at 0, 430, or 1200 mg/kg-day for 36 weeks. Treated animals had urinary calculi and bladder tumors (Ogasawara et al. 1995). Co-treatment with 5% or 10% NaCl decreased the formation of both the calculi and bladder tumors. The increase in water intake caused by the NaCl, which increased urinary volume diluting the urinary melamine, was thought to be responsible for reduction in the precipitation of urinary melamine. Thus, decreased calculi formation was considered to be directly related to the reduction in bladder tumors.

4. Reproductive and Developmental Effects

Pregnant rats were given intraperitoneal injections of 70 mg/kg on GD's 5 and 6, 8 and 9, or 12 and 13 (Thiersch 1957). The author reported that there were no toxic effects or gross malformations in the fetuses.

5. Neurotoxicity

No neurotoxicity data were available.

6. Toxicity under the FHSA

Melamine may be considered acutely toxic under the FHSA, although it is not highly toxic. The oral LD_{50} in F344 rats was between 3,200 and 3,800 mg/kg (NTP 1983). Aqueous solutions of melamine were non-irritating to the skin and eyes of animals. The dry solid was mildly irritating to the eyes of rabbits. Thus, pure melamine is possibly a mild eye irritant. Based on limited data, there is no evidence of teratogenicity in animals. Reproductive toxicity and neurotoxicity were not studied.

Dietary melamine caused the formation of papillomas and transitional cell carcinomas in the bladder epithelium of high-dose male F344 rats in a two-year bioassay. The incidence of tumors was not increased in low-dose males rats, female rats, or in mice. There was a significant statistical association between the presence of tumors and calculi. The tumors are considered to result from chronic irritation from the bladder calculi, followed by epithelial hyperplasia (Burin et al. 1995; Meek et al. 2003; Rodent Bladder Carcinogenesis Working Group 1995).

Although the formation of bladder calculi is possible in humans, calculi are typically not present in the human urinary tract for a sufficient length of time to cause epithelial hyperplasia (Burin et al. 1995; Meek et al. 2003; Rodent Bladder Carcinogenesis Working Group 1995). Calculi in humans are typically quickly voided as a result of the anatomy of the urinary tract and the upright, bipedal nature of humans. Therefore, the mode of action by which melamine induces bladder tumors in male rats is considered to be not relevant to humans. Because melamine caused tumors only at high doses in one sex and species, and the mode of action is probably not relevant to humans, melamine may be considered a possible human carcinogen, based on limited evidence in animals. The finding that melamine is possibly carcinogenic to humans does not satisfy the regulatory definition of "toxic."

III. DOSE RESPONSE

A. Tris(1,3-Dichloro-2-Propyl) Phosphate (TDCP)

The LOAEL for non-cancer effects in the two-year rat study was 5 mg/kg-d (Biodynamics 1981; EPA 2005a; NRC 2000). Histopathological effects were observed in several organs, including the liver, kidney, spleen, parathyroid, testes, epididymes, and seminal vesicle. Histopathological effects that were significantly elevated at the LOAEL included seminal vesicle atrophy and decreased seminal vesicle secretory product in males, and erythroid/myeloid metaplasia of the spleen in females (Table 3). A benchmark dose was not calculated in this case, due to an incomplete database. With the exception of liver and kidney, only a subset of animals from each dose/sex group were subjected to complete histopathology (see also NRC 2000). None of the available dose-response models was able to adequately fit the available data. Therefore, an uncertainty factor approach was used. An overall uncertainty factor of 1,000 was applied to the LOAEL, including 10-fold for animal to human extrapolation, 10-fold for inter-individual variability, and 10-fold because a no-observed-adverse-effect level (NOAEL) was not established. This results in an ADI level of 0.005 mg/kg-d.

The NRC subcommittee derived a reference dose (RfD)* of 0.005 mg/kg-d (NRC 2000). However, the NRC subcommittee applied uncertainty factors of 10-fold for animal to human extrapolation, 3-fold for inter-individual variability, 10-fold because a NOAEL was not established, and 3-fold for an incomplete database. The CPSC chronic hazard guidelines do not provide for an additional uncertainty factor for an incomplete database (CPSC 1992). The default factor for inter-individual variability used by CPSC and others is 10-fold. The NRC subcommittee applied a 3-fold factor for inter-individual variability in this case, because there was no evidence of increased sensitivity of juvenile animals from developmental toxicity studies (NRC 2000). They did not indicate what studies were lacking from the database.

The CPSC staff derived a cancer unit risk (potency) estimate for TDCP, based on the incidence of hepatocellular tumors (carcinoma and adenoma) and tumors of the renal cortex. Benign tumors of the testes and adrenal cortex were not included, because no malignancies were present in the organ sites. Thus, it does not appear that these particular tumors would progress to malignancy. In addition, testicular interstitial cell adenomas have a high background rate in rats, and their relevance to human cancer risk is uncertain (CPSC 1992, p. 46636). Hepatocellular carcinomas and adenomas were combined,† because hepatocellular adenomas are known to progress to carcinomas (CPSC 1992, p. 46636). Tumor incidence data for males and females were combined, because their unit risks differed by less than a factor of two when computed separately (CPSC 1992, p. 46654).

Animal bioassay data were fitted to the multistage model using Global83 (Howe and Crump 1983; Crump 1984), as described in the chronic hazard guidelines (CPSC 1992, p. 46654). The

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* Both the acceptable daily intake (ADI) and reference dose (RfD) are estimates of the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects.

† That is, the incidence is the number of animals with adenoma or carcinoma.

unit risk was based on the maximum likelihood estimate of extra risk, that is, the linear term (q_1) in the model:

$$P(D) = 1 - e^{-(q_0 + q_1 D + q_2 D^2 \cdots q_i D^i)} \quad (1)$$

where: P(D), lifetime cancer risk at dose D; q_i, model parameters to be fitted. The parameters q_i must be non-negative, and *i* is an integer with a value from 1 to 9.

Unit risks for liver and renal tumors were calculated separately and then added, as described in the CPSC chronic hazard guidelines (CPSC 1992, p. 46654). The unit risks in animals for liver and renal tumors, respectively, were 6.4×10^{-3} and 2.5×10^{-3} $(mg/kg\text{-}d)^{-1}$. The overall unit risk in animals was 8.9×10^{-3} $(mg/kg\text{-}d)^{-1}$.

Animal-to-human extrapolation was by the surface area correction, that is, the unit risk is proportional to body weight to the three-quarters power (CPSC 1992, p. 46654; EPA 1992). Mean terminal body weights in untreated controls were 612 g in males and 386 g in females (Freudenthal and Henrich 2000). The average of males and females was 499 g. Thus, humans are estimated to be 3.5-fold more sensitive than the rats:

$$F = \left(\frac{BW_{animal}}{BW_{human}} \right)^{-1/4} = \left(\frac{0.499}{75} \right)^{-1/4} = 3.5 \quad (2)$$

where: F, interspecies conversion factor, unitless; BW_{animal}, average animal body weight (0.499 kg); and BW_{human}, average human body weight (75 kg).

By this methodology, the unit risk for kidney and liver tumors combined is estimated to be 0.031 $(mg/kg\text{-}d)^{-1}$:

$$Q = F \cdot q_1 = 3.5 \times 8.9 \times 10^{-3} = 3.1 \times 10^{-2} \left(mg/kg - d \right)^{-1} \quad (3)$$

where: Q, unit risk in humans, $(mg/kg\text{-}d)^{-1}$; F, interspecies conversion factor, unitless; and q_1, unit risk in animals, $(mg/kg\text{-}d)^{-1}$.

The NRC subcommittee derived a unit risk of 0.06 $(mg/kg\text{-}d)^{-1}$ (NRC 2000). This was based on the incidence of testicular interstitial cell tumors in the same bioassay cited here (Biodynamics 1981; Freudenthal and Henrich 2000). According to the NRC report, the testicular tumors were used because they were the most sensitive tumor site (NRC 2000). The subcommittee calculated the LED_{10}, that is, the 95th lower confidence limit of the dose at which the cancer risk is 0.1, using the multistage model. Linear extrapolation was then used to calculate the unit risk.

B. Triphenyl Phosphate (TPP) and Phenol Isopropylated Phosphate (PIP)

Previously, the CPSC staff concluded that there were sufficient data to derive ADI values for three of the 10 aromatic phosphates or mixtures that the staff reviewed: Santicizer 148 (roughly 90% isodecyl diphenyl phosphate), 0.01 mg/kg-d; TCP isomers, 0.05 mg/kg-d; and 2-ethylhexyl diphenyl phosphate, 1.0 mg/kg-d (Bittner et al. 2001; Ferrante 1999b) (see Table 2). The NRC subcommittee derived an RfD of 0.07 mg/kg-d for TCP isomers.

The CPSC staff also concluded that there was insufficient information to derive ADI levels for PIP or TPP (Ferrante 1999a; Bittner et al. 2001). There are no subchronic or chronic studies with full histopathology for either compound. For the purpose of the present preliminary risk assessment, estimated exposures to these compounds will be compared to the ADI values for other aromatic phosphates, which range from 0.01 to 1.0 mg/kg-d (Bittner 2001; Bittner et al. 2001; Ferrante 1999a) (see Table 2).

C. Octyl Tetrabromobenzoate (OTB)

There is insufficient information to derive an ADI value for OTB. No structurally related compounds were identified that had sufficient data to derive an ADI.

D. Melamine

Melamine did not satisfy the FHSA definition of "toxic." Therefore, an ADI cannot be calculated. A quantitative risk assessment is not needed to determine whether products containing melamine may be hazardous (CPSC 1992).

IV. EXPOSURE AND BIOAVAILABILITY

As in previous risk assessments involving FR chemicals, exposure was estimated by analyzing various exposure scenarios (Babich and Thomas 2001; Thomas and Brundage 2006). This was accomplished through a combination of laboratory studies and mathematical models. Dermal, inhalation, and oral exposure routes were included. Inhalation exposure considered both vapor phase and particles. Separate exposure estimates were made for adults and small children.

A. Laboratory Studies

The CPSC staff conducted laboratory studies to estimate the possible migration of FR chemicals from upholstery foam (Cobb and Bhooshan 2005). Experiments utilized a mock-up consisting of a 9x9x½-inch (23x23x1.25 cm) sheet of plywood supporting a 3-inch thick slab of the FR-treated upholstery foam to be tested (Figure 4). The foam was covered by a standard non-FR fabric (50-50 cotton-polyester blend). No interliner or batting was present in the mock-up, because some upholstered furniture does not have these components. The presence of an interliner or batting might be expected to reduce migration. The mock-up and experimental methods were adapted from the staff exposure and risk assessment for mattresses (Cobb 2005; Thomas and Brundage 2005). Three foam samples that could be used to meet the draft flammability standard were tested. Foam "S" contained 6.6% TDCP, foam "Y" contained 3.5% TDCP and 11% melamine, and foam "Z" contained 6% FM-550™ and 2.8% melamine (Cobb and Chen 2005). Foams S and Z contained the highest TDCP and FM-550™ concentrations among the samples available for testing.

To study the potential for dermal and oral exposure, the mock-up was wetted with 25 mL of isotonic saline solution (0.9% NaCl). Two 55 mm diameter pieces of #2 filter paper were placed on the wetted portion and covered with weights. The weights were 2 inches in diameter (5.1 cm) and weighed 3.14 pounds (1.4 kg), resulting in one pound per square-inch (psi) of pressure (6.9 kPa). After 6 hours, the filter paper was removed and analyzed for FR content. The test was repeated with the same foam sample for up to eight consecutive days. FR chemical in the filter paper is assumed to be available for transfer to the skin or mouthing by children (Thomas and Brundage 2006). FR chemicals on the skin can be absorbed percutaneously or transferred to the mouth by hand-to-mouth activity. Foams S and Y were each tested once. Two specimens of foam Z were tested, one for 4 days and the second for 8 days. The average migration from each iteration was used to estimate exposure.

Experiments were also conducted to estimate the release of particles containing FR chemicals into air (Cobb and Bhooshan 2005). Mock-ups were subjected to repetitive impaction with an air-driven piston attached to a 4-inch diameter semi-spherical form. Mock-ups were impacted 100,000 times at a rate of 1 per second and 3 pounds per square inch pressure. Tests were done inside a closed, inflatable glove bag supported by a metal frame, with a volume of 216 L. Recirculated air was continuously sampled at a rate of 2 L per minute to collect inhalable particles. The total amount of particulate phase FR chemical collected was assumed to be released during the lifetime of the furniture. Duplicate samples of foam S and Z were tested. Foam Y was not subjected to this test. Three filter cassettes were used in each test.

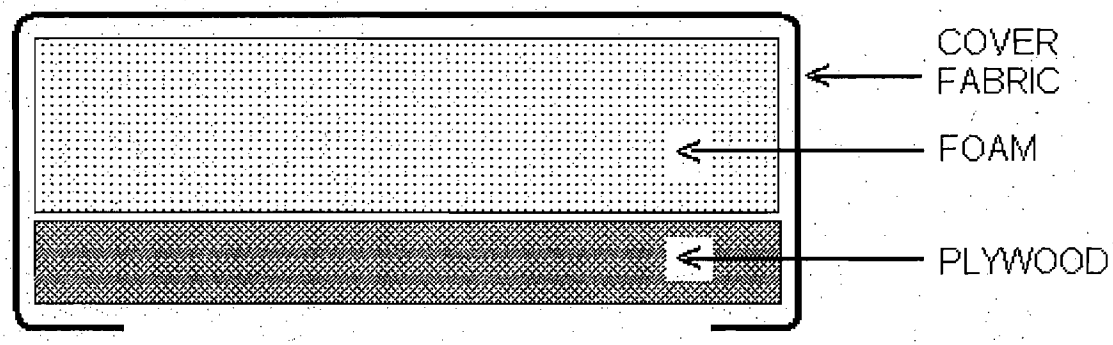

Figure 4. Mock-up for exposure studies

B. Calculations

To estimate dermal exposure, it is assumed that an external liquid phase facilitates the transfer of FR chemical from the foam to the surface of the cover fabric and then to the skin (compare NRC 2000). During normal use, that is, while sitting on furniture, perspiration is assumed to be the liquid phase. The amount of FR chemical migrating to the fabric surface was measured in the laboratory as described above (Cobb and Bhooshan 2005).

The ADI and unit risk values for the chemicals of interest are derived from oral studies. The bioavailability, that is, the fraction of the applied dose that is absorbed, generally varies for different exposure routes. Therefore, in calculating exposure and risk from dermal and inhalation exposure, it is appropriate to make a route-to-route adjustment to account for differences in bioavailability (Babich and Thomas 2001).

The average daily dose (ADD) from dermal exposure was calculated by:

$$ADD_D = \frac{M \cdot F \cdot S \cdot K_T \cdot T}{W \cdot B} \quad (1)$$

where: ADD_D, average daily dose from dermal exposure, mg/kg-d; M, amount of FR chemical that migrates to the fabric surface, mg/cm^2; F, fraction of liquid phase transferred to the skin, unitless; S, skin surface area exposed, cm^2; K_T, percutaneous absorption rate, h^{-1}; T, exposure duration, h/d; W, body weight, kg; and B is the oral bioavailability, unitless.

Oral exposure may occur either by direct mouthing of furniture cover fabric or by hand-to-mouth activity. As with dermal exposure, migration of FR chemical from foam is assumed to be mediated by an external liquid phase, in this case saliva. The amount of FR chemical migrating to the surface of the cover fabric was estimated in laboratory studies as described above (Cobb

and Bhooshan 2005). The average daily dose from indirect mouthing, that is, hand-to-mouth activity was calculated by:

$$ADD_{OH} = \frac{M \cdot F \cdot S_H \cdot F_H}{W} \quad (2)$$

where: ADD_{OH}, average daily dose from hand-to-mouth activity, mg/kg-d; M, amount of FR chemical that migrates to the fabric surface, mg/cm^2; F, fraction transferred from the fabric to the hand; S_H, surface area of the hand that is mouthed, cm^2; F_H, hand to mouth transfer factor, d^{-1}; and W, body weight, kg.

The average daily dose from direct mouthing activity was calculated by:

$$ADD_{OM} = \frac{M \cdot S_M \cdot F_M}{W} \quad (3)$$

where: ADD_{OM}, average daily dose from direct mouthing activity, mg/kg-d; M, amount of FR chemical that migrates to the fabric surface, mg/cm^2; S_M, surface area of fabric that is mouthed, cm^2; F_M, fabric to mouth transfer factor, d^{-1}; and W, body weight, kg.

The total oral exposure is given by:

$$ADD_O = \frac{M(F \cdot S_H \cdot F_H + S_M \cdot F_M)}{W} \quad (4)$$

where: ADD_O, average daily dose from oral exposure, mg/kg-d; M, amount of FR chemical that migrates to the fabric surface, mg/cm^2; F, fraction transferred from the fabric to the hand; S_H, surface area of the hand that is mouthed, cm^2; F_H, hand to mouth transfer factor, d^{-1}; S_M, surface area of fabric that is mouthed, cm^2; F_M, fabric to mouth transfer, d^{-1}; and W, body weight, kg.

Inhalation exposure may occur from the release of semi-volatile FR chemicals into the vapor phase or from the release of FR-containing particles during normal wear or aging. The release of FR-containing particles was measured in the laboratory as described above (Cobb and Bhooshan 2005). The total amount of particle-bound FR chemical released during the accelerated wear test was assumed to be released over the lifetime of the furniture (compare Thomas and Brundage 2005). Inhalation exposures were estimated using a two-zone mass balance model, where zone 1 is the breathing zone (Thompson and Thompson 1990) and zone 2 is the room containing the upholstered furniture. The source of FR emissions is located in the breathing zone.

The average daily dose from inhalation exposure to vapor phase FR chemical was calculated by:

$$ADD_{IV} = \left(C_{V1} \cdot T_1 + C_{V2} \cdot T_2\right) \cdot \left(\frac{I}{W \cdot B}\right) \quad (5)$$

where: ADD_{IV}, average daily dose from inhalation exposure of vapor phase chemical, mg/kg-d; C_{V1}, C_{V2}, concentrations of vapor phase FR chemical in zones 1 and 2, respectively, mg/m^3; T_1, T_2, exposure duration in zones 1 and 2, h; FR chemical in zone 2, the living or family room, mg/m^3; exposure duration in zone 2, h; I, average inhalation rate, m^3/h; W, body weight, kg; and B, oral bioavailability, unitless.

The concentration of vapor phase chemical was calculated from a two-zone mass-balance model (NRC, 1981). This model assumes that the outdoor concentration of FR chemical is zero, and that the breathing zone (zone 1) does not exchange directly with the outdoor air. Thus, the concentrations of vapor phase FR chemical in zones 1 and 2 are given by:

$$dC_{V1} = \left[A(C_{V2} - C_{V1}) + E_V - K_V \cdot V_1 \cdot C_{V1} \right] \left[dT / V_1 \right]$$
$$dC_{V2} = \left[A(C_{V1} - C_{V2}) - K \cdot V_2 \cdot C_{V2} - K_V \cdot V_2 \cdot C_{V2} \right] \left[dT / V_2 \right] \quad (6)$$

where: C_{V1}, C_{V2}, concentrations of vapor phase FR chemical in zones 1 and 2, respectively, mg/m^3; K, air infiltration rate, h^{-1}; V_1, volume of zone 1 (breathing zone); A, inter-zone air exchange rate, m^3/h; E_V, source strength for vapor phase chemical, in zone 1, mg/h; V_1, V_2, volumes of zones 1 and 2, m^3; K_V, decay rate for vapor phase chemical; and T, time, h.

This system of two differential equations was solved by Euler's method. The concentrations at 12 hours were used to calculate exposure, as steady-state is generally reached before this time.

The source strength for vapor phase FR, E_V, was estimated by means of a mathematical model (Babich and Thomas 2001) that is essentially similar to the model described by the NRC subcommittee (NRC 2000). The difference is that the CPSC staff separated the source strength and mass-balance expressions. This allowed us to change from a 1-zone to a 2-zone model, for example. The source strength is given by:

$$E_{V1} = \frac{C_{Sat}}{\frac{1}{K \cdot V} + \frac{H}{1 \times 10^{-4} \cdot S_P \cdot D_{Air}}} \quad for\ T_{Max} \geq P\ years$$
$$E_{V2} = \frac{T_{Max} \cdot E_{V1}}{P} \quad for\ T_{Max} < P\ years \quad (7)$$

where:

$$T_{Max} = \left[\frac{10{,}000 \cdot FRL \cdot H}{C_{Sat} \cdot D_{Air} \cdot 8{,}766} \right] \cdot \left[1 + \frac{1 \times 10^{-4} \cdot S_P \cdot D_{Air}}{A \cdot V \cdot H} \right] \quad (8)$$

and where: T_{max}, maximum time that vapor phase FR can be released at the estimated rate, y; 1x10^{-4}, to convert from cm^2 to m^2; 10,000, to convert from mg/cm^2 to mg/m^2; FRL, FR chemical loading rate, mg/cm^2; H, boundary layer height, m; C_{sat}, saturation concentration

in air, mg/m^3; D_{air}, diffusivity in air, m^2/h; 8766, number of hours per year; S_P, surface area of foam in a suite of furniture, cm^2; K, air infiltration rate, h^{-1}; V, room volume, m^3; P, product lifetime, y; and E_V, source strength, mg/h.

C_{Sat} was estimated as previously (Babich and Thomas 2001):

$$C_{Sat} = \frac{MM \cdot VP \cdot 1 \times 10^6}{R \cdot Temp} \tag{9}$$

where: MM, molecular mass, grams/mole; VP, vapor pressure, torr; 1x10^6, to convert from grams per liter to mg/m^3; R, gas constant, 62.4 torr-L/mole-degree Kelvin; Temp, temperature (298°K).

D_{Air} was estimated as described by Schwope et al. (1989):

$$D_{Air} = \frac{3.3}{\left(2.5 + MM^{1/3}\right)^2} \cdot \frac{3600}{10{,}000} \tag{10}$$

where: D_{Air}, m^2/h, MM, molecular mass, grams/mole; and 3600/10,000 is to convert from cm^2/sec to m^2/hour.

The average daily dose from inhalation of particle-bound FR chemical is given by:

$$ADD_{IP} = \left(C_{P1} \cdot T_1 + C_{P2} \cdot T_2\right) \cdot \left(\frac{I}{W \cdot B}\right) \tag{11}$$

where: ADD_{IP}, average daily dose from inhalation exposure of particle-bound chemical, mg/kg-d; C_{P1}, C_{P2}, concentrations of particle-bound FR chemical in zones 1 and 2, mg/m^3; T_1, T_2, exposure duration in zones 1 and 2, h/d; I, average inhalation rate, m^3/h; W body weight, kg; and B, oral bioavailability, unitless.

The concentrations in each zone (C_{P1}, C_{P2}) were calculated from the two-zone mass balance model:

$$\begin{aligned} dC_{P1} &= \left[A\left(C_{P2} - C_{P1}\right) + E_P - K_P \cdot V_1 \cdot C_{P1}\right]\left[dT/V_1\right] \\ dC_{P2} &= \left[A\left(C_{P1} - C_{P2}\right) - K \cdot V_2 \cdot C_{P2} - K_P \cdot V_2 \cdot C_{P2}\right]\left[dT/V_2\right] \end{aligned} \tag{12}$$

where: C_{P1}, C_{P2}, concentrations of particle-bound FR chemical in zones 1 and 2, respectively, mg/m^3; A, inter-zone air exchange rate, m^3/h; E_P, source strength for particle-bound FR chemical, mg/h; K, air infiltration rate, h^{-1}; K_P, particle decay (deposition) rate, h^{-1}; and V_1, V_2, volumes of zones 1 and 2.

As with equation (6) above, this system of two differential equations was solved by Euler's method. The concentrations at 12 hours, were used to calculate exposure, as steady-state is generally reached before this time.

The source strength (E_P) was estimated by:

$$E_P = \frac{M_P \cdot F_P}{24 \cdot 365 \cdot P} = \frac{M_P \cdot F_P}{8{,}760 \cdot P} \tag{13}$$

where: E_P, source strength, mg/h; M_P, mass of FR chemical released in the impaction experiment, mg; F_P, scaling factor, unitless; 24, hours per day; 365, days per year; and P, average product lifetime, years. F_P is the ratio of the total surface area of foam in the product to the area of the mock-up.

The overall ADD value was obtained by summing the ADD values for each route of exposure:

$$ADD = ADD_O + ADD_D + ADD_I \tag{14}$$

where: ADD, total average daily dose from all routes, mg/kg-d; ADD_O, ADD_D, and ADD_I, average daily doses from oral, dermal, and inhalation exposure, respectively, mg/kg-d.

The lifetime average daily dose (LADD) was calculated from the ADD as follows:

$$LADD = \frac{ADD \cdot Y}{L} \tag{15}$$

where: LADD, lifetime average daily dose; ADD, average daily dose, mg/kg-d; Y, number of years the consumer is exposed, y; L, average life expectancy, y.

C. Input Parameters

1. General Parameters

General input parameters are summarized in Table 5. The average lifetime of a suite of upholstered furniture (P), 15 years, was estimated by industry representatives (Babich and Thomas 2001; NRC 2000). For the purpose of uncertainty analysis, 5 and 25 years were assumed to be reasonable lower and upper bounds, respectively. The average number of years of exposure to upholstered furniture (Y) is not necessarily the same as the average product life. A consumer may be exposed to several different types of furniture, which may be treated with different FR chemicals or none at all. For calculating cancer risk, it was assumed that adults are exposed to the same FR treatments for a lifetime, which is the most conservative approach. This assumption is only relevant to cancer risk. The average furniture lifetime (15 years) may be considered a reasonable lower bound for exposure duration.

For children, an exposure duration (Y) of two years, the first two years of life, was assumed. Children are most likely to place objects in their mouths between 3 months and 12 months of age; mouthing activity declines significantly by 24 months of age (Greene 1998). Mouthing activity is one of the principal quantifiable differences between children and adults that may affect exposure to FR chemicals. The body weight, surface area, and respiration rate are also different in children.

The average life expectancy (L) and average body weight (W) for adults are from the EPA "Exposure Factors Handbook" (EPA 1997). Body weights for males and females 45-54 years old were averaged (EPA 1997 Tables 7-4, 7-5). The 5th, 50th, and 95th percentile values were used as the lower bound, best estimate, and upper bound, respectively. Children's body weights and lengths were for one-year-olds (CDC, 2000). The 5th, 50th, and 95th percentile values for boys and girls were averaged, and used as the lower bound, best estimate, and upper bound, respectively.

The foam surface area, S_P, was estimated as 2.8 m^2 (28,000 cm^2) for a suite of furniture including a sofa, love seat, and chair (Babich and Thomas 2001). The seating area and seat back were assumed to be constructed with polyurethane foam. The average foam mass, W_P, for a similar suite of furniture was estimated by the Directorate for Economic Analysis* to be 15 kg.

Table 5. General Input Parameters

Parameter		Best Estimate	Lower Bound	Upper Bound	Reference
Body weight, W, kg		72	50	101	EPA 1997, Tables 7-4, 7-5
	Children	10	8.3	12	CDC 2000
Life expectancy, L, y		75	ND	ND	EPA 1997
Years of exposure, Y, y		75	15	75	Assumptions; see text
	Children	2	2	2	
Product lifetime, P, y		15	5	25	Estimates; see text
Product (foam) surface area, S_P, cm^2		28,000	17,000	56,000	
Product (foam) mass, W_P, kg		25	ND	ND	

ND, not determined.

2. Dermal Exposure

For estimating dermal exposure, it was assumed that the consumer is lying on a sofa and wearing a short-sleeved shirt and short pants (Babich and Thomas 2001; Smith 2000). Due to the 3-dimensional shape of the limbs, it was assumed that roughly one-third of the exposed surface area was in contact with the furniture surface at a given time. Thus, the surface areas for the lower leg and arms were combined, then divided by three. For adults, median values for males and females were averaged (EPA 1997, Table 6-2, 6-3). The lower bound for adults was

* Personal communication from Charles Smith, Directorate for Economic Analysis.

assumed to be one-third the combined surface areas for the hands and feet. The upper bound was assumed to be one-third the total surface area. Parameters relating to dermal exposure are summarized in Table 6.

For children, surface areas for body parts were available as the percentage of the total surface area. Mean values for the age groups <1 year and 1 to <2 years old were averaged (EPA 1997, Table 6-8). Data for the lower leg were not provided; thus, the lower leg was assumed to be 40% of the area of the entire leg, which is the case for adults. For children <2 years old, the total surface area was not available (EPA 1997, Tables 6-6 and 6-7). Thus, the average total surface area was calculated as follows (EPA 1997, Equation 6A-8 and Table 6A-1):

$$S_{Total} = 0.02667 \cdot L^{0.3821} \cdot W^{0.53937} \quad (16)$$

where: S_{Total}, total body surface area, m^2; L, length, cm; and W, body weight (kg).

Absolute surface areas were computed from percent areas and the total surface area. Upper and lower bounds were analogous to the adult values.

An average exposure of 4 hours per day (T) for adults was estimated (Babich and Thomas 2001; Smith, 2000) from compiled activity data. This is the amount of time that adults and older children spend in "indoor/leisure" activities (EPA 1997, Table 15-8 to 15-10). Exposure durations of 0.5 hours and 16 hours were assumed as reasonable lower and upper bounds. Children up to 2 years old spend approximately 3 hours per day in "passive leisure" activities (EPA 1997 Table 15-12). An average exposure duration of 3 hours per day, with lower and upper bounds of 0.5 and 12 hours per day, was assumed. The total daily exposure duration may, in fact, be divided among several events. However, dividing the total exposure among several events does not affect the exposure calculation.

Table 6. Input Parameters for Estimating Dermal Exposure

Parameter	Best Estimate	Lower Bound	Upper Bound	Reference
Fabric to skin transfer, F	0.13	0.024	0.84	See Table 8
Surface area of exposed skin, S, cm^2	1,700	700	6,000	EPA 1997; Smith 2000; see text
Children	350	190	2,400	
Exposure duration, T, h/d	4	0.5	16	
Children	3	0.5	12	

ND, not determined.

Chemical-specific input parameters are summarized in Table 7. Liquid-mediated migration to the fabric surface (M) was measured as described above. FR chemical migrating to the filter paper was assumed to be deposited on the surface of the cover fabric and, therefore, available for transfer to the skin. The components of FM-550™ could not be quantified individually (Cobb

and Bhooshan 2005). Migration measurements for FM-550™ are based on the OTB component. Thus, OTB is a surrogate for TPP and PIP. The average migration from each iteration (that is, from each daily measurement) was used to estimate exposure. Results from the two TDCP-containing samples (n=16) were averaged. Results from two FM-550™-treated specimens were also averaged (n=12).

Table 7. Chemical-Specific Input Parameters

Parameter	Symbol	Units	TDCP	TPP	PIP	OTB
FR mass percent in foam	FRW	mass percent	5.1 [a,b]	6.8 [a,c]	6.8 [a,c]	6.8 [a]
FR loading rate [d]	FRL	mg/cm^2	46	36 [c]	36 [c]	36
Total FR in product [d]	FRT	mg	$1.3x10^6$	$1x10^{6}$ [c]	$1x10^{6}$ [c]	$1x10^6$
Migration to liquid phase [e]	M	mg/cm^2	$1.5x10^{-4}$ [a,b]	$4.5x10^{-5}$ [a,c]	$4.5x10^{-5}$ [a,c]	$4.5x10^{-5}$ [a]
Mass released from impaction [a, f]	M_P	mg	0.0015	<0.0004 [c]	<0.0004 [c]	<0.0004
Oral bioavailability	B	unitless	0.9 [g]	1.0 [h]	1.0 [h]	1.0 [h]
Dermal absorption rate	K_T	h^{-1}	0.08 [i]	0.1 [j]	0.1 [j]	0.01 [k]
Acceptable daily intake	ADI	mg/kg-d	0.005 [l]	0.01—1.0 [m]	0.01—1.0 [m]	ND [n]
Cancer unit risk	Q	$(mg/kg-d)^{-1}$	0.031 [l]	NA	NA	NA

[a] Measured by CPSC staff (Cobb and Bhooshan 2005; Cobb and Chen 2005).

[b] Average from two samples, foam S and foam Y.

[c] Value is for the OTB component of FM-550™. Individual components were not quantified.

[d] Estimated from the mass percent.

[e] Average migration from up to 8 repeated tests on consecutive days with the same sample (Cobb and Bhooshan 2005). In calculating the average, non-detects were regarded as one-half the detection limit. Converted from mg to mg/cm^2 by dividing by the area of the filter paper, 24 cm^2.

[f] Five of 6 TDCP replicates (foam S) and 5 of 5 FM-550™ replicates (foam Z) were below the method detection limit. Non-detects were regarded as one-half the detection limit.

[g] Matthews and Anderson 1979.

[h] Default assumption.

[i] Estimated from *in vitro* data (Hughes et al. 2001).

[j] Estimated from *in vivo* data for *o*-tricresyl phosphate (Nomeir and Abou-Donia 1984).

[k] Assumed (see text).

[l] Estimated from two-year study in rats (Biodynamics 1981; Brandwene 2001; Freudenthal and Heinrich 2000).

[m] Range of values for aromatic phosphates (Bittner et al. 2001; Ferrante 1999a).

[n] NA, not applicable; ND, not determined.

FR chemical migration from the foam to the filter paper depends, in part, on the volume of liquid phase (25 mL) and the pressure (1 psi) applied to the filter paper. The 1 psi was based on the average peak pressure of an adult lying on a mattress (reviewed in Midgett 2005). Upholstered furniture is generally less firm than mattresses, and the consumer is typically seated. Sitting would increase the pressure, relative to lying down. However, some of the weight may be supported by the side and back of the furniture, and the feet. The relatively soft furniture would probably distribute the weight more evenly.

The amount of liquid phase was based on the amount of perspiration excreted from the body during an 8-hour period, about 0.05 mL per square centimeter of skin area (reviewed in Thomas and Brundage 2005). However, the average exposure duration of adults to upholstered furniture is estimated as 4 hours. Therefore, the amount of saline solution may tend to overestimate exposure.

Several authors have studied the transfer of various chemicals from treated textiles to human or animal skin. These studies were used to estimate the fraction of FR chemical transferred from the fabric surface (represented by the filter paper) to the skin, that is, the fabric-to-skin transfer efficiency (Table 8). Substances included dust particles (Rodes et al. 2001), glyphosate and malathion (Wester et al. 1996), permethrin (Snodgrass 1992), riboflavin (Cohen-Hubal et al. 2005), and TRIS (Ulsamer et al. 1978b). For the present risk assessment, the overall mean transfer efficiency 0.13 was assumed to be the best estimate for the transfer efficiency, with the minimum (0.024) and maximum (0.84) as the lower and upper bounds. The percutaneous absorption rate (K_T) is described below (Bioavailability).

Table 8. Fraction of Test Substance Transferred from Textile to Skin

Substance	Fraction Transferred		Textile	Skin	Method	Reference
	Dry	Moist				
Dust	0.061	0.050	Carpet	Human	*In vivo*	Rodes et al. 2001
Glyphosate	0.056	0.254	Cloth	Human	*In vitro*	Wester et al. 1996
Malathion	0.068	0.837	Cloth	Human	*In vitro*	Wester et al. 1996
Permethrin	0.031	0.037	Cloth	Rabbit	*In vivo*	Snodgrass 1992
Riboflavin	0.024	0.050	Carpet	Human	*In vivo*	Cohen-Hubal et al. 2004
TRIS	0.046	0.060	Cloth	Rabbit	*In vivo*	Ulsamer et al. 1978b
Mean	0.048	0.22				
Overall Mean	0.13					
Minimum	0.024					
Maximum	0.84					

3. Oral Exposure

Oral exposure to FR chemical may occur either indirectly by transfer of FR chemical from the fabric surface to the hand or directly by mouthing of upholstered furniture. FR chemical on the hand may be ingested by hand-to-mouth contact or by transfer of FR chemical from the hands to food or other objects. Indirect transfer is assumed to occur in both children and adults, while direct mouthing is assumed to occur primarily in children. The relevant surface area for hand-to-mouth activity (S_H) was assumed to be the ventral surface (palm) of the hands or roughly one-half the surface area of the hands. Parameters are summarized in Table 9. One-tenth of the best estimate, roughly equivalent to the fingertips, was assumed as a reasonable lower bound. The entire surface area of both hands, the theoretical maximum, was used as an upper bound.

Table 9. Input Parameters for Estimating Oral Exposure

Parameter	Best Estimate	Lower Bound	Upper Bound	Reference
Mouthed surface area, hand, S_H, cm^2	450	45	900	EPA 1997; see text
Children	130	13	260	
Hand to mouth transfer, F_H, d^{-1}	0.4	0.03	7	Hatlelid 2003
Mouthed surface area, fabric, S_M, cm^2	0	0	50	Assumption; see text
Children	10	0	50	CPSC 1983; NRC 2000
Fabric to mouth transfer, F_M, d^{-1}	0.4	0.03	7	Hatlelid 2003

ND, not determined.

For adults, the median surface area of the hands is 0.099 m^2 in men and 0.0817 m^2 in women (EPA 1997, Tables 6-2 and 6-3). Averaging the two values and dividing by two gives 0.045 m^2 or 450 cm^2. For children aged <1 and 1 to <2 years old, the hands represent 5.3 and 5.7 % of the total body surface area, respectively (EPA 1997, Table 6-8). The total surface area was calculated as 0.48 m^2 (equation (16)). Multiplying the total surface area by 5.5 % (the average of 5.3 and 5.7) and dividing by two gives roughly 0.013 m^2 or 130 cm^2.

For direct mouthing, a surface area (S_M) of 10 cm^2 was assumed for children. The CPSC staff has previously used values of 10 or 11 cm^2 for direct mouthing (Babich et al. 2004; Babich and Thomas 2001; CPSC 1983). Upper and lower bounds of 0 and 50 cm^2 were assumed. The upper bound is the value used by the NRC subcommittee (NRC 2000). For adults, zero cm^2 was assumed as both the best estimate and lower bound, while 50 cm^2 was assumed for the upper bound.

Few data on the transfer of chemicals from the hand to the mouth (F_H) or fabric to the mouth (F_M) are available. For playground equipment made from pressure-treated lumber, the CPSC staff used an average value of 0.43 for hand-to-mouth transfer, with a range of 0.03 to 7 (Hatlelid 2003). This was derived from the ratio of soil loading on the hands and soil ingestion (Hatlelid 2003; Lee 1990a,b). This value was for a 24-hour period, independent of the number of individual mouthing events. The upper bound is greater than one, because the hand can be

"re-loaded" during the course of a day. For the present risk assessment, an average value of 0.4, with lower and upper bounds of 0.03 and 7, was assumed for both hand-to-mouth and fabric-to-mouth transfer.

4. Inhalation Exposure

Long term average inhalation rates (I)—0.55 m^3/h for adults and 0.24 m^3/h for children (EPA 1997, Table 5-23)—were used, as the exposure duration includes sleep and other indoor activities (Table 10). The adult value is the average for men and women. The lower and upper bounds for adults are for rest and light activities, respectively. For children, the upper and lower bounds were assumed to be proportional to the adult values.

Consumers spend an average of 16 hours in their residence each day (EPA 1997, p.15-17). Thus, it was assumed that the total exposure duration for inhalation exposure is 16 h/d. The time in the breathing zone was assumed to be the time spent sitting on upholstered furniture, that is, the exposure duration for dermal exposure (see above, Table 6). Thus, the exposure duration in the breathing zone (T_1) was 4 h/d for adults and 3 h/d for children. The time spent outside the breathing zone (T_2) was assumed to be the difference between the total exposure duration (16 hours) and T_1, or 12 hours for adults and 13 hours for children. The lower and upper bounds for T_1 are also the same as for dermal exposure. The lower and upper bounds for the total time indoors were assumed to be 8 and 24 h/d, respectively. The total of T_1 and T_2 in any given instance cannot exceed 24 hours. Thus, the lower and upper bounds for T_2 were assumed to be 8 h/d and 23.5 h/d.

A breathing zone of 1 m^3 is typically used for estimating the exposure of a consumer to volatile compounds, such as arts and crafts materials (Thompson and Thompson 1990). For the present case, the breathing zone was assumed to include a 1 meter-high rectangle over the horizontal seating area of a suite of furniture. The horizontal surface area was estimated as 1.7 m^2 (see above). Thus V_1 was 1.7 m^3. One-half this value was assumed as the lower bound, and twice this value as the upper bound. The best estimate of the room volume (V_2) was assumed as the upper bound. The room volume (V_2) was estimated as 120 m^3. This represents the volume of an open living room, dining room, and kitchen in a typical 1,500 ft^2 ranch home (CPSC 1990). One-half the value (60 m^3) was assumed to be the lower bound. The upper bound was assumed to be the median total volume for U.S. residences (EPA 1997, Table 17-1).

The average (whole-house) air infiltration rate (K) is the median value for all seasons and all regions of the U.S. (Koontz and Rector 1993, Table 2). The 5^{th} and 95^{th} percentiles were used as lower and upper bounds.

The air exchange rate between the breathing zone and the room (A) was estimated as 17 m^3/h. The breathing zone is an abstract volume of space, bounded only by the seating area and seat back of the furniture. Thus, the air exchange rate was assumed to be greater than the exchange between rooms or between indoors and outdoors. The value for A is equivalent to 10 air changes per hour (10 h^{-1}). That is, the air in the breathing zone is replaced 10 times per hour or once every 6 minutes. This is, in turn, equivalent to a linear air flow ("cross-breeze") of 17 m/h or 0.01 miles per hour. For comparison, whole house air infiltration rates are typically on the order

of 2 h^{-1} with the windows open (Koontz and Rector 1993). Outdoors, the air exchange rate may range from 10 to over 100 h^{-1}. A one mile per hour breeze is equivalent to 160 h^{-1}. The lower and upper bounds were assumed to be equivalent to 1 and 20 air changes per hour.

Table 10. Input Parameters for Estimating Inhalation Exposure

Parameter	Best Estimate	Lower Bound	Upper Bound	Reference
Average inhalation rate, I, m^3/h	0.55	0.4	1.0	EPA 1997; Table 5-23
Children	0.24	0.17	0.4	
Exposure duration, in the breathing zone, T_1, h/d	4	0.5	16	EPA 1997, Table 5-23; see text
Children	3	0.5	12	
Exposure duration, outside the breathing zone, T_2, h/d [a]	12	8	23.5	
Children	13	8	23.5	
Volume, breathing zone, V_1, m^3	1.7	0.85	3.4	Assumption; see text
Volume, room, V_2, m^3	120	60	320	EPA 1997, Table 17-1; see text
Air infiltration rate, K, h^{-1}	0.4	0.15	1.7	Koontz & Rector 1993
Inter-zone air exchange rate, A, m^3/h	17	1.7	34	Assumption; see text
Particle decay rate, K_D, h^{-1}	2.0	0.5	4.0	EPA 1997; Table 17-13
Vapor phase decay rate, K_V, h^{-1}	0	0	1	Assumption; NRC 2000
Scaling factor, F_P	60	30	120	Calculated from S_P
Boundary layer height, H, m	0.01	0.001	0.1	NRC 2000; see text

[a] The total of T_1 and T_2 in any given case may not exceed 24 hours.

Exposure to particles deposited in the nasopharyngeal (~5-30 μm), tracheobronchial (~1-5 μm), and alveolar (~1 μm) regions of the respiratory tract are all relevant, because the chemicals of interest are systemic toxicants. Deposition rates for particles roughly corresponding to these size ranges include: 0.5 h^{-1} (1-5 μm), 1.4 h^{-1} (5-10 μm), and 2.4 h^{-1} (10-25 μm) (EPA 1997, Table 17-13). Particles released from the wear and aging of upholstered furniture components are likely to include a broad range of particle sizes (Stevens et al. 2003). A decay rate of 2 h^{-1}, representing particles from 1 to 25 μm in diameter, was considered as the best estimate. The lower and upper bound values were for particles in the size ranges 1-to-5 μm and >25 μm, respectively.

The mass of FR chemical released from impaction (M_P) was measured as described above. Non-detects were assumed to equal one-half the detection limit (Table 7). All of the FM-550™ samples and most of the TDCP samples were non-detects. The components of FM-550™ could not be quantified individually (Cobb and Bhooshan 2005). Therefore, the total migration of FM-550™ was used to calculate exposure to each component (TPP, PIP, or OTB). The total amount of FR chemical retained by the filters was assumed to be released over the lifetime of the product (15 years).

The seating area and seat back are assumed to be constructed with polyurethane foam. This area was estimated as 2.8 m^2 (28,000 cm^2) for a suite of furniture including a sofa, love seat, and chair (Babich and Thomas 2001). The mock-up has a surface area of 530 cm^2 or 0.053 m^2 (9x9 inch). Thus, the scaling factor was calculated by dividing 2.8 m^2 by 0.053 m^3, which is approximately 60-fold. The lower bound assumed a suite of furniture in which only the horizontal seating area included foam. The upper bound assumed two suites of furniture in the home, such as in a living room and family room. The source strength (E_P) was calculated using equation (13).

Physico-chemical properties are summarized in Table 11. The saturation concentration (C_{sat}) was calculated from the vapor pressure using equation (9). The diffusivity was estimated with equation (10). The boundary layer height was the value used by the NRC subcommittee (NRC 2000). Values of 0.1-fold and 10-fold were assumed as lower and upper bounds. The decay rate for vapor phase FR was assumed to equal zero (Babich and Thomas 2001; NRC 2000). A value of one was assumed as an upper bound.

Table 11. Physico-Chemical Properties

Parameter	Symbol	Units	TDCP	TPP	PIP [a]	OTB
Molecular mass	MM	g/mol	430.91	326.29	368.37	549.93
Vapor pressure	VP	torr	$2.7x10^{-5}$ [b]	$6.3x10^{-6}$ [c, d]	$3.5x10^{-7}$ [d,e]	$<1x10^{-6}$ [f]
Saturation concentration in air [g]	C_{sat}	mg/m^3	0.63	0.24	0.0069	0.015
Diffusivity in air [h]	D_{air}	m^2/h	0.012	0.013	0.013	0.010
Octanol-water partition coefficient [i]	Log K_{OW}	unitless	3.65 [d]	4.59 [d]	5.31 [d]	8.75, 12.0 [j]

[a] Data are for *o*-IPDP, a component of PIP.

[b] Extrapolated from data for TDCP-treated foam in Cobb and Bhooshan 2005.

[c] Extrapolated from empirical data (EPA 2005a, SRC 2006).

[d] Syracuse Research Corp. physical properties database, accessed through the National Library of Medicine ChemID database. June 2006.

[e] Model estimate.

[f] Upper bound model estimate (EPA 2005a). One-half this value ($5x10^{-7}$) was used to estimate C_{sat}.

[g] Calculated from the vapor pressure and molecular mass.

[h] Estimated as described in Schwope et al. 1989.

[i] The log K_{OW} is not required for the risk assessment. It is included for discussion purposes.

[j] Model estimates for the two component isomers (EPA 2005a).

The physical properties of *o*-IPDP (28108-99-8) were used for PIP. IPDP is a component of PIP, which is a complex substance. The molecular mass of OTB was calculated from the molecular formula (Cobb and Bhooshan 2005). The vapor pressure of OTB is an upper bound estimate from a mathematical model (EPA 2005a). Because it is an upper-bound, one-half the upper bound estimate was used to estimate exposure. The vapor pressure of IPDP is an estimated value (SRC 2006). The log K_{OW} values for the two OTB isomers are model estimates. The log K_{OW}'s of TDCP, TPP, and IPDP are empirical (SRC 2006). Log K_{OW} is not required for the risk

assessment calculations, but is useful in comparing the other physico-chemical and biological properties of environmental contaminants.

The effective saturation concentration of TDCP was extrapolated from data in Cobb and Bhooshan (2005). TDCP-treated foam was placed in a sealed flask. The TDCP concentration in the air inside the flask was measured at 65°C and 120°C. The concentration at 25°C was estimated from a plot of the logarithm of the concentration against the reciprocal of the absolute temperature, by analogy to the Clausius-Clapeyron equation:

$$m = \frac{\ln C_2 - \ln C_1}{\left(\frac{1}{T_2} - \frac{1}{T_1}\right)} \tag{17}$$

where: m, slope; and C_1, C_2, concentrations (mg/m^3) at temperatures T_1 and T_2 (°K).

The concentration at 25°C (273°K) was then calculated from:

$$\ln C = m\left(\frac{1}{T} - \frac{1}{T_1}\right) + \ln C_1 \tag{18}$$

5. Bioavailability

In general, little information on the bioavailability of the chemicals of interest was available. The ADI values are based on oral studies. The oral bioavailability of TDCP was reported to be about 90% (Matthews and Anderson 1979). In the absence of appropriate data, the bioavailabilities of the other chemicals are assumed to be 100% (CPSC 1992).

Inhalation may also contribute to total FR chemical exposure. In the absence of appropriate data, 100% of inhaled FR chemical, whether in the vapor phase or bound to particles, is assumed to be absorbed.

Dermal exposure is likely to be a significant exposure route for FR chemicals in upholstered furniture. The percutaneous absorption rate for *o*-TCP, estimated from animal studies, was used for the aromatic phosphates TPP and PIP. A dose of 50 mg radiolabeled *o*-TCP dissolved in acetone was applied to the clipped necks of cats (Nomeir and Abou-Donia 1984). The acetone was evaporated under a stream of air. The application site was approximately 10 cm^2. Thus, the specific dose was approximately 5 mg/cm^2. After 12 hours, 73% of the applied dose was absorbed. Assuming 1st-order kinetics, the absorption rate was about 0.1 h^{-1}:

$$FA = 1 - e^{-(K_T \cdot T)} \tag{19}$$

where: FA, fraction of applied dose absorbed, unitless; K_T, percutaneous absorption rate (or transfer rate), h^{-1}; and T, time, h.

Solving for K_T:

$$K_T = \frac{-\ln(1-FA)}{T} \quad (20)$$

The percutaneous absorption rate (K_T) for TDCP was derived from *in vitro* studies using hairless mouse skin (Hughes et al. 2001). It is the same value used previously by the CPSC staff (Babich and Thomas 2001). ^{14}C-Labeled TDCP was applied to the skin by solvent deposition. At 24 hours, from 39 to 57% of the applied dose was found in the receptor fluid. From 28 to 34% was found in the skin, after unabsorbed TDCP was removed by thorough washing. The percentage absorption at 24 hours, including TDCP in both the receptor fluid and skin, was used to estimate the percutaneous absorption rate. Total absorption of TDCP ranged from 73 percent to 85 percent of the applied dose, depending on the applied dose (0.014 to 0.14 μg/cm^2). Based on 85 percent absorption at 24 hours, and assuming 1st-order kinetics, the percutaneous absorption rate for TDCP was estimated as 0.08 h^{-1}.

No data relating to percutaneous absorption of OTB were available. The OTB isomers are expected to be extremely hydrophobic, with predicted log K_{ow} values of 8.75 and 12 (EPA 2005a). The molecular mass (549.93) is relatively high. Percutaneous absorption generally increases with increasing K_{ow} and decreases with increasing molecular mass (Potts and Guy 1992). Other brominated FR chemicals reviewed by the CPSC staff include DBDPO and HBCD. HBCD was absorbed at a rate of approximately 0.003 h^{-1} (Babich and Thomas 2001), based on *in vitro* studies (Hughes 2000). In the same study, DBDPO was absorbed at a rate of 0.001 h^{-1} to 0.01 h^{-1} (Babich and Thomas 2001), depending on the applied dose (Hughes 2000; Hughes et al. 2001). In the absence of appropriate data, a value of 0.01 h^{-1} was assumed for OTB.

V. RISK

The potential risk from non-cancer endpoints is evaluated by calculating the hazard index (HI), which is the ratio of the ADD to the acceptable daily intake (ADI), that is:

$$HI = \frac{ADD}{ADI} \tag{21}$$

where: HI, hazard index, unitless; ADD, overall average daily dose, mg/kg-d; and ADI, acceptable daily intake, mg/kg-d.

When the HI is greater than one, the product or exposure scenario under consideration is considered to present a hazard to consumers.

The lifetime individual excess cancer risk was calculated by:

$$R = Q \cdot LADD \tag{22}$$

where: R, lifetime individual excess cancer risk; Q, unit cancer risk or cancer potency, $(mg/kg\text{-}d)^{-1}$; and LADD, lifetime average daily dose, mg/kg-d.

The results of the exposure and risk assessment are summarized in Table 12.

A. Tris(1,3-Dichloro-2-Propyl) Phosphate (TDCP)

The estimated HI for non-cancer effects is 2 in adults and 5 in children. Thus, the estimated exposure exceeds the ADI. The estimated lifetime individual cancer risk in adults is 300 per million, based on a lifetime of exposure to furniture with similar levels of TDCP. The estimated cancer risk in children from two-years of exposure to TDCP-containing furniture is 20 per million. Cancer risks greater than one-in-a-million are considered relevant for regulatory consideration under the CPSC chronic hazard guidelines (CPSC 1992). In both adults and children, inhalation of vapor phase TDCP contributed the largest fraction, over 95%, of the total exposure. TDCP exposure from the dermal and oral routes, is based on migration measurements using a mock-up (Cobb and Bhooshan 2005). TDCP exposure from inhalation of airborne particles is also based on studies with the mock-up. The exposure estimate for vapor phase TDCP is based on a mathematical model. Empirical data on inhalation exposure to vapor phase TDCP are needed to assess whether TDCP may present a hazard to consumers.

Table 12. Exposure and Risk

Result	TDCP		TPP [a]		PIP [a]		OTB	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
ADD (mg/kg-d)	$9.5x10^{-3}$	$2.6x10^{-2}$	$1.8x10^{-3}$	$4.8x10^{-3}$	$1.8x10^{-4}$	$4.0x10^{-4}$	$2.0x10^{-4}$	$5.5x10^{-4}$
Percent of total:							0	
Dermal	1.7	0.7	3.6	1.4	35.3	17.4	2.9	1.1
Oral, indirect	0.5	0.4	0.9	0.6	8.5	7.8	7.7	5.7
Oral, direct	0.0	0.2	0.0	0.4	0.0	4.6	0.0	3.4
Inhalation, vapor [b]	97.7	98.7	95.6	97.5	56.2	70.1	89.4	89.8
Inhalation, particles	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ADI (mg/kg-d)	0.005	0.005	0.01—1 [c]	0.01—1 [c]	0.01—1 [c]	0.01—1 [c]	ND [d]	ND [d]
HI	2	5	0.002—0.2 [c]	0.005—0.5 [c]	0.0002—0.02 [c]	0.0004—0.04 [c]	ND [d]	ND [d]
LADD (mg/kg-d)	$9.5x10^{-3}$	$7.4x10^{-4}$	$1.8x10^{-3}$	$1.3x10^{-4}$	$1.8x10^{-4}$	$1.1x10^{-5}$	$2.0x10^{-4}$	$1.5x10^{-5}$
Cancer risk per million	300	20	ND	ND	ND	ND	ND	ND

ADD, average daily dose; HI, hazard index; LADD, lifetime average daily dose; ND, not determined.

[a] Dermal, oral, and airborne particle exposures are based on measurements of the OTB component of FM-550™ (Cobb and Bhooshan 2005).

[b] Inhalation exposure to vapor phase FR chemical is based on a mathematical model (see text).

[c] Insufficient data were available to derive ADI's for TPP and PIP. The HI's are based on the range of ADI values for other aromatic phosphate plasticizers (Ferrante 1999a).

[d] Insufficient data were available to derive an ADI for OTB or related compounds.

B. Triphenyl Phosphate (TPP)

There was insufficient information to derive an ADI for TPP. Therefore, the ADI's for other aromatic phosphates (0.01 to 1 mg/kg-d) were used to calculate a range of hazard indices. The estimated HI, based on non-cancer effects, ranges from 0.002 to 0.2 in adults and 0.005 to 0.5 in children. As with TDCP, inhalation of vapor phase TPP contributed the largest fraction of the total estimated exposure, over 95%. TPP exposure from the dermal and oral routes is based on migration measurements for the OTB component of FM-550™ (Cobb and Bhooshan 2005). TPP exposure from inhalation of airborne particles is based on measurements of OTB release. Exposure to vapor phase TPP was estimated by a mathematical model. Empirical data are needed to estimate TPP exposure more accurately.

C. Phenol Isopropylated Phosphate (PIP)

There was insufficient information to derive an ADI for PIP. Therefore, the ADI's for other aromatic phosphates (0.01 to 1 mg/kg-d) were used to calculate a range of hazard indices. The estimated HI, based on non-cancer effects, ranges from 0.0002 to 0.02 in adults and 0.0004 to 0.04 in children. Inhalation of vapor phase PIP contributed about 56% of the total estimated exposure in adults and 70% in children. Dermal exposure contributed about 19% in adults and 9% in children. PIP exposure from the dermal and oral routes is based on migration measurements for the OTB component of FM-550™ (Cobb and Bhooshan 2005). PIP exposure from inhalation of airborne particles is based on measurements of OTB release. Exposure to vapor phase PIP was estimated by a mathematical model. Empirical data are needed to estimate PIP exposure more accurately.

D. Octyl Tetrabromobenzoate (OTB)

There was insufficient information to derive an ADI for OTB or related compounds. The average daily dose was estimated to be 2.0×10^{-4} mg/kg-d in adults and 5.5×10^{-4} in children. Over 89% of the total estimated exposure in adults and children was from inhalation of vapor phase OTB. Exposure to vapor phase OTB was estimated by a mathematical model.

E. Sensitivity Analysis

A sensitivity analysis of the exposure model was conducted to assess variability and uncertainty. This was done by individually adjusting input parameters to the lower or upper bound, and then determining the relative effect (ratio) on the estimated average daily dose (ADD). This was done in a route-specific manner. That is, the effect of varying parameters that apply to multiple routes was based on the total ADD. The effects of varying parameters that apply only to dermal, oral, or inhalation exposure, were based on ADD_D, ADD_O, and ADD_I, respectively. TDCP exposure was the basis for the sensitivity analysis (Table 13).

Table 13. Route-Specific Sensitivity Analysis

Parameter	Best Estimate	Lower Bound		Upper Bound	
		Value	Ratio	Value	Ratio
All Routes					
Body weight, W, kg	72	50	1.4	105	0.7
Years of exposure, Y, y	75	15	1.0	75	1.0
Product lifetime, P, y	15	5	1.0	25	1.0
Product surface area, S_P, cm^2	28,000	17,000	0.6	56,000	1.9
Dermal					
Fabric to skin transfer, F	0.13	0.024	0.2	0.84	6.5
Surface area of exposed skin, S, cm^2	1,700	700	0.4	6,000	3.5
Exposure duration, T, h/d	4	0.5	0.1	16	4.0
Oral					
Mouthed surface area, hand, S_H, cm^2	450	45	0.1	900	2.0
Hand to mouth transfer, F_H, d^{-1}	0.4	0.03	0.1	7	17.5
Mouthed surface area, fabric, S_M, cm^2	0	0	--	50	1.8
Fabric to mouth transfer, F_M, d^{-1}	0.4	0.03	1.0	7	1.0
Fabric to skin transfer, F	0.13	0.024	0.2	0.84	6.5
Inhalation					
Average inhalation rate, I, m^3/h	0.55	0.4	0.7	1.0	1.8
Exposure duration, breathing zone, T_1, h/d	4	0.5	0.5	24	2.7
Exposure duration, outside breathing zone, T_2, h/d	12	8	0.8	23.5	0.9 [a]
Scaling factor, F_P	60	30	1.0	120	1.0
Breathing zone volume, V_1, m^3	1.7	0.85	1.0	3.4	1.0
Room volume, V_2, m^3	120	60	1.5	320	0.9
Air infiltration rate, A, h^{-1}	0.4	0.15	1.6	1.7	0.6
Inter-zone exchange rate, m^3/h	17	1.7	4.7	34	0.8
Particle decay rate, K_D, h^{-1}	2.0	0.5	1.0	4.0	1.0
Vapor phase decay rate, K_V, h^{-1}	0	0	--	1	0.6
Boundary layer height, H, m	0.01	0.001	2.9	0.1	0.1

This sensitivity analysis is based on the estimated TDCP exposure to adults. The ratio is the relative effect on the ADD when parameters are varied individually from the best estimate to the lower or upper bound. Ratios for parameters affecting all routes are based on the total ADD. Ratios for the dermal, oral, and inhalation parameters are based on ADD(D), ADD(O), and ADD(I), respectively.

[a] T_1 was set to the lower bound so that $T_1 + T_2 \leq 24$ h.

Varying the parameters that affect all routes—body weight, years exposed, product lifetime, and product surface area—had very small effects on the overall average daily dose. Varying these parameters generally had a small effect on cancer risk, except that the cancer risk is directly related to years of exposure (Table 14).

Table 14. Sensitivity of Cancer Risk to Selected Parameters

Parameter	Best Estimate	Lower Bound		Upper Bound	
		Value	Ratio	Value	Ratio
Body weight, W, kg	72	50	1.4	105	0.7
Years of exposure, Y, y	75	15	0.2	--	--
Product lifetime, P, y	15	5	1.0	25	1.0
Product surface area, S_P, cm^2	28,000	17,000	0.6	56,000	1.9

This sensitivity analysis is based on the estimated cancer risk in adults exposed to TDCP in upholstery foam. The ratio is the relative effect on risk when parameters are varied individually from the best estimate to the lower or upper bound.

By varying the dermal exposure parameters, the estimated dermal exposure ranged from roughly one-tenth to 7 times the best estimate (Table 13). The hand-to-mouth transfer factor had a substantial effect on oral exposure; the estimated oral exposure ranged from one-tenth to almost 20-fold, relative to the best estimate. Most of the inhalation parameters had less than a 3-fold effect on exposure.

Changing the inter-zone air exchange rate to the lower bound resulted in a 5-fold increase in exposure. Increasing the boundary layer height to the upper bound reduced exposure to one-tenth. Reducing the boundary layer height to the lower bound increased exposure by 3-fold.

A sensitivity analysis was also performed using input parameters for children (Table 15). For children, the fabric-to-mouth transfer factor had a significant effect, due to the direct mouthing scenario. Raising this factor to the upper bound resulted in a 12-fold increase in oral exposure. The fabric-to-skin transfer factor also had a substantial effect on oral exposure, due to indirect mouthing. All other results (not shown) were essentially similar to those for adults.

Generally, the chemical-specific input parameters (Table 7) were based on limited data. For example, the amount of chemical migrating to the liquid phase (M) and the amount released from impaction were (M_P) measured with a limited number of samples and limited number of replicates. Thus, the uncertainty in these values cannot be assessed. The equations for dermal (1) and oral (4) exposure are linear and, therefore, the variance in migration (M) would lead to a proportional effect in dermal and oral exposure. Although the equations for inhalation exposure are nonlinear, the concentrations in the breathing zone (C_1) and the room are (C_2) are proportional to the source strength (not shown). The source strength (E_P) for particle-phase FR chemical is proportional to the amount released by impaction (M_P), as in equation (13). Thus,

the variance in the amount released from impaction (M_P) would lead to a proportional effect in the inhalation exposure to particles.

Information on the uncertainties of the physico-chemical properties (Table 11) is generally not available. The precisions of empirical measurements are not usually reported. Several of the values used here are model estimates or extrapolated values, including the vapor pressures for TPP, PIP, and OTB. The saturation concentration in air (C_{sat}) and diffusivity (D_{air}) were estimated.

Table 15. Sensitivity Analysis of Oral Exposure to Children

Parameter	Best Estimate	Lower Bound		Upper Bound	
		Value	Ratio	Value	Ratio
Oral					
Mouthed surface area, hand, S_H, cm^2	130	13	0.4	260	1.7
Hand to mouth transfer, F_H, d^{-1}	0.4	0.03	0.4	7	12
Mouthed surface area, fabric, S_M, cm^2	10	0	0.6	50	2.5
Fabric to mouth transfer, F_M, d^{-1}	0.4	0.03	0.7	7	7.3
Fabric to skin transfer, F	0.13	0.024	0.5	0.84	4.5

This sensitivity analysis is based on the estimated oral TDCP exposure to children. The ratio is the relative effect on the oral average daily dose when parameters are varied individually from the best estimate to the lower or upper bound.

VI. DISCUSSION

This risk assessment should be considered preliminary due to data gaps in several areas. Insufficient toxicity data were available to derive ADI's for TPP, PIP, and OTB. Only three foam samples were subjected to exposure testing, and the components of FM-550™ (TPP, PIP, and OTB) could not be individually quantified. No empirical data on emissions of vapor phase chemicals were available. Thus, a mathematical model was used to estimate exposure. However, the lack of vapor pressure data for TPP, PIP, and OTB severely limits the usefulness of the vapor phase model. Data on vapor phase emissions are critical, because inhalation of vapor phase FR chemical appears to contribute the greatest portion of the total exposure.

A. Toxicity

There was a general lack of inhalation toxicity studies, which is significant because inhalation appears to be the most important route of exposure.

There are no data relating to possible interactions among aromatic phosphates and OTB. There are no data to evaluate the relative sensitivity of children or juvenile animals to any of the FR chemicals under consideration. Exposure to carcinogens early in life or *in utero* may lead to an increased cancer risk (reviewed in EPA 2005b). No adjustments were applied to account for the possible increased sensitivity of children (CSPC 1992). Thus, the risk assessment for children is based only on differences in exposure. The HI's calculated for children are conservative in that they are based on a two-year exposure period, while the ADI's used to calculated the HI's are generally based on a lifetime of exposure.

The cancer risk in children represents the contribution to the lifetime risk from exposure during the first two years of life. Because only children are exposed by direct mouthing, the risk from this route of exposure may be added to the risk in adults to obtain the true lifetime risk. However, the estimated cancer risk from mouthing is negligible in comparison to the lifetime cancer risk in adults

1. Firemaster™ 550 (FM-550™)

Limited toxicological and bioavailability data are available for the components of FM-550™. No toxicological data on the mixture is available. There was insufficient information to derive ADI values for TPP, PIP, or OTB. TPP and PIP are members of a broader class of compounds, the aromatic phosphate plasticizers, that has been reviewed by the CPSC staff. ADI values for other aromatic phosphates, including mixtures, were used as surrogates for TPP and PIP. These other ADI values ranged from 0.01 to 1.0 mg/kg-d (Ferrante 1999a; Bittner et al. 2001). Although several aromatic phosphates have been studied in subchronic studies, only two have been tested in chronic studies. The CPSC staff has nominated the aromatic phosphates, as a class, for additional testing by the National Toxicology Program (NTP).

There was insufficient information to assess the acute toxicity of OTB, and no information on chronic toxicity. Furthermore, no toxicity data for structurally-related chemicals were identified. Thus, an ADI and HI could not be estimated.

2. Melamine

Melamine has been well studied in comparison to TPP, PIP, and OTB, including two-year studies in mice and rats. The CPSC staff concludes that melamine does not satisfy the regulatory definition of "toxic." However, we note that the database includes no neurotoxicity or reproductive studies, and only one limited developmental screen.

3. Tris(1,3-Dichloro-2-Propyl) Phosphate (TDCP)

TDCP has also been well studied, including a two-year study in rats. This study was sufficient to derive a chronic ADI level and cancer potency estimate. However, inhalation appears to be the primary route of exposure, whereas the bioassay was by the oral route. Differences in absorption (i.e., bioavailability), distribution, and metabolism between exposure routes could significantly affect toxicity and carcinogenicity.

No information on the inhalation bioavailability of TDCP was available. Therefore, we made the default assumption that 100% of inhaled TDCP was absorbed. To the extent that the bioavailability is less than 100%, the inhalation exposure and resulting risk will be overestimated.

Any chemical absorbed through the lungs will enter the systemic circulation prior to being metabolized in the liver. Thus, systemic exposure to the parent compound may be increased. The effect of increased systemic exposure depends on whether the parent compound or a metabolite is the proximate toxic species. If the parent compound is responsible for either carcinogenicity or non-cancer effects, then the effective dose and its resulting risk may be underestimated.

TDCP is metabolized to the diester plus 1,3-dichloro-2-propanol (Nomeir et al. 1981; Sasaki et al. 1984). The alcohol is further metabolized to 3-chloro-1,2-propanediol. TDCP is also directly conjugated by glutathione. The species responsible for toxicity and carcinogenicity are unknown, and need not be the same. TDCP is a phosphotriester and , thus, could be an alkylating agent. TDCP formed adducts with protein and DNA in mice (Morales and Matthews 1980). Thus, direct alkylation by TDCP might contribute to either organ toxicity or carcinogenicity. TDCP is, at best, weakly mutagenic. The diester was not mutagenic in *Salmonella*, while the diol metabolite was weakly mutagenic (Gold et al. 1978). However, the putative metabolite 1,3-dichloro-2-propanone was a strong direct-acting mutagen. This suggests that a metabolite may be responsible for carcinogenicity and/or toxicity.

Overall, TDCP was weakly genotoxic in bacteria and in some mammalian systems. It was generally less mutagenic than the structural analog TRIS. Although TDCP is only weakly genotoxic, the metabolite 1,3-dichloro-2-propanol was mutagenic in Salmonella TA-100 without metabolic activation. Furthermore, TDCP was shown to bind to DNA *in vivo*. Therefore, the possibility of a genotoxic mode of action for carcinogenicity cannot be dismissed. On the other hand, the absence of the putative metabolite 1,3-dichloro-2-propanone could explain why TDCP is less mutagenic than TRIS.

In any case, genotoxicity is not a prerequisite for applying a linear dose-response model to estimate cancer risk. Linearity at low doses is the default assumption in the absence of convincing evidence to the contrary (CPSC 1992). An understanding of the mode of action or other information relating to the dose response would be needed to support a different dose response model. Obtaining sufficient data is generally very difficult and may require years of research (Meek et al. 2003).

If the default assumption of low-dose linearity is not applied, then the cancer risk could be assessed by a variety of methods, including a non-linear risk model, such as the probit or logit, or by an uncertainty factor approach, applying uncertainty factors to either the NOAEL or a benchmark dose (BMD). For example, using the benchmark dose approach, the dose at which the extra risk is 5% (BMD_{05}) was estimated to be 7.7 mg/kg-d, using the multistage model (equation (1)) and data for renal tumors. Applying the default uncertainty factors for interspecies differences in sensitivity and to protect sensitive individuals, the ADI for cancer would be 0.08 mg/kg-d. Comparing this to the ADD (Table 12), the HI for cancer would be 0.1 in adults and 0.3 in children. Thus, by this approach TDCP probably would not present a cancer hazard to consumers.

The percutaneous absorption rate of TDCP was estimated from an *in vitro* study using hairless mouse skin (Hughes et al. 2001). When human skin is not available, skin from the hairless mouse is preferred for *in vitro* studies (Bronaugh et al. 2005). The studies were performed by U.S. EPA staff at the request of CPSC (Hughes et al. 2001). TDCP was applied to the skin in an acetone solution. The acetone was evaporated under a stream of air. Acetone is not likely to damage the skin due to the limited contact time.

The cumulative amount of TDCP in the receptor fluid at 24 hours was added to the amount remaining in the skin after thoroughly removing TDCP from the surface of the skin. This is to estimate systemic exposure, since hydrophobic compounds do not partition well into the aqueous receptor fluid (Bronaugh et al. 2005). It is assumed that TDCP in the skin would be absorbed *in vivo*. In this case, more than half of the TDCP was in the receptor fluid (Hughes et al. 2001). Thus, including only TDCP in the receptor fluid would reduce the estimated dermal dose by less than 2-fold.

In vivo, the amount of chemical remaining within the skin may be considered as a reservoir that may be absorbed over time. If absorption from this reservoir is sufficiently slow, the reservoir may be lost due to normal exfoliation. Thus, net systemic absorption is the result of two competing events—absorption and exfoliation. As discussed above, over half of TDCP was found in the receptor fluid. Thus, even if the entire reservoir is lost due to exfoliation, which occurs over a period of about 14 days, then the effect on systemic absorption would be less than two-fold.

Percutaneous absorption rates may be greater with animal than human skin (Bronaugh 2005). The percutaneous absorption of a related FR, tris(chloropropyl)phosphate (TCPP), was tested *in vitro* using human skin and an aqueous vehicle (Maas 2005a). TCPP was absorbed at roughly the same rate as TDCP. This suggests that the hairless mouse model is a reasonable surrogate for

human skin, and that the acetone in the Hughes et al. (2001) study probably did not adversely affect skin permeability.

While *in vitro* studies are generally predictive of *in vivo* percutaneous absorption rates, *in vivo* studies are preferred. *In vitro* studies may under-predict absorption of hydrophobic compounds, because hydrophobic compounds do not partition well into the aqueous receptor fluid (Bronaugh 2005). TDCP was reported to be readily absorbed through the skin of rats *in vivo*, although the study was not designed to measure the absorption rate (Nomeir et al. 1981). Ulsamer et al. (1979, 1980) reported that TDCP was absorbed at twice the rate of TRIS in rabbits. No other details were reported. In another study, however, 15% of the applied dose of TRIS was absorbed through the skin of rabbits in 96 hours (Ulsamer et al. 1978a). Thus, TRIS was apparently absorbed at a much lower rate *in vivo* in rabbits (0.0016 h^{-1}) than TDCP was absorbed *in vitro* (0.035 h^{-1}) using mouse skin.

B. Exposure

The exposure assessment is limited in that only a small number of foam samples were tested, as well as the limited number of tests on each sample. Therefore, it is uncertain whether these results may be applicable to other foam samples treated with the same chemicals, and how precisely the results can be replicated. However, with the two TDCP samples, migration was roughly proportional to the TDCP content. Foam S (TDCP) and Foam Z (FM-550™) were selected because they contained the highest FR concentrations available. Furniture treated with the FR chemicals was not available for testing.

The aromatic phosphate components of FM-550™ generally were not quantified in the exposure studies. The migration data used to estimate dermal and oral exposure, as well as data on the release of airborne particles, are based on the OTB component of FM-550™ (Cobb and Bhooshan 2005). Therefore, the exposures for these routes are uncertain.

Except for mass-balance models in general, the laboratory or mathematical models used to estimate exposure have not been validated by comparison with reliable exposure data, such as from field studies. Appropriate data do not exist. The mathematical models generally assume conditions of chemical equilibrium and steady-state. These assumptions are commonly used, in part, because dynamic models are much more complicated. However, the assumption of equilibrium or steady-state conditions may over-estimate exposure if steady-state is not reached during exposure. If exposure depends on a series of intermittent events that begin each time one sits on an upholstered chair, then it is possible that steady-state is not achieved. This might be the case for dermal exposure, for example. On the other hand, if exposure is a continuous process, then steady-state is more likely to be achieved. This might apply to the inhalation of vapor phase FR chemicals, which does not require direct contact with the product. The indoor concentration of vapor phase FR would vary to a degree, depending on ventilation and other factors, but it might be relatively stable over time.

1. Dermal Exposure

The method for estimating the potential for dermal exposure was adapted from exposure studies for mattress filling materials (Thomas and Brundage 2006). The method was intended to provide a realistic exposure estimate. However, the appropriate pressure and amount of liquid phase are difficult to estimate, and the values used for mattresses might not be optimal for upholstered furniture. No interliner or batting was present in the mock-up, because some upholstered furniture does not have these components. The presence of an interliner or batting might be expected to reduce migration. As with mattresses, these migration data were also used to estimate oral exposure.

Recently, the migration of TCPP from polyurethane foam was studied using artificial sweat as a solvent (Maas 2005b). TCPP is structurally related to TDCP. A stack of 15 filters was placed directly on the foam. Total TCPP released was 5.6 $\mu g/cm^2$ with no pressure applied and 9.2 $\mu g/cm^2$ with pressure applied (Maas 2005b, Appendix 1). In comparison, the migration of TDCP was 0.15 $\mu g/cm^2$, as measured by the CPSC staff (Cobb and Bhooshan 2005). The different results may be due, in part, to differences in methodology and the type of foam. In addition, TCPP is about 10-fold more water-soluble than TDCP (IPCS 1998).

2. Inhalation Exposure

The potential for release of particles containing FR chemicals was also assessed using a method developed for mattresses. For the most part, FR chemicals were not detectable in airborne particles released when the mock-up was subjected to impaction. Therefore, it does not appear that inhalation of particles would contribute significantly to consumer exposure. This is not unexpected, since the foam is resilient and is an internal component. However, aged or in-service foams were not tested.

The source strength of vapor phase FR chemical was estimated using a mathematical model that is essentially similar to the model described by the NRC Subcommittee on Flame Retardant Chemicals (NRC 2000; see also Babich and Thomas 2001). The model includes several conservative assumptions, including the lack of affinity of the FR for the foam and barriers to vaporization of FR chemical. In practice, the FR chemicals may have an affinity for the foam matrix due to covalent or non-covalent binding. The foam, interliner, and cover fabric may all impede the release of FR chemical into air.

Also in accordance with the NRC study, we assumed that there are no sinks or decay processes to attenuate the indoor concentration due to the lack of data to estimate the rates of these processes. Semi-volatile chemicals are known to be absorbed by other household furnishings or materials, including carpets, draperies, and wallboard. This tends to reduce the indoor air levels of these chemicals. Vapor phase FR chemicals may also be adsorbed to airborne particles or break down to other substances. Therefore, the model is expected to overestimate exposure to vapor phase FR chemical. Furthermore, in the absence of bioavailability data, 100% absorption and retention of vapor phase chemicals was assumed.

Although the vapor phase model includes a number of conservative assumptions, the source strength calculation is based on diffusion in a static environment. This may be most applicable to a scenario in which upholstered furniture sits in an unoccupied room. However, typical use of the furniture such as sitting, fidgeting, or active child play will apply mechanical actions that might increase the release of vapor phase FR chemical, as well as particles.

The reliance on a purely theoretical model to estimate vapor phase exposure is of concern, because inhalation was the major route of exposure for all of the compounds under consideration, accounting for between 75% and 99% of the total estimated exposure (Table 12). Furthermore, there is considerable uncertainty in the vapor pressures of several of the FR chemicals, which are primary input values to the model. Empirical vapor pressures are not available for PIP and OTB. The vapor pressures for PIP (SRC 2006) and OTB (EPA 2005a) were estimated from mathematical models. The vapor pressure of TPP was extrapolated from empirical data (EPA 2005a; SRC 2006).

Several different vapor pressures have been reported for TDCP. The empirical vapor pressure was reported to be 0.01 torr at 30°C (IPCS 1998) and 0.024 torr at 20°C (Supresta 2006). Another report gives the empirical vapor pressure at temperatures ranging from 50 to 500°F (Akzo 1998), from which we interpolated the vapor pressure to be 0.15 torr at 20°C and 0.2 torr at 25°C. Other authoritative sources cite estimated vapor pressures of $1x10^{-6}$ torr (EPA 2005a) and $7.4x10^{-8}$ torr at 25°C (SRC 2006). The CPSC staff measured the concentration of TDCP vapor at 65°C and 120°C in a sealed flask containing either liquid TDCP or TDCP-treated foam (Bhooshan and Cobb 2005). From these data we extrapolated the vapor pressure at 25°C as 0.0014 torr. In addition, the effective vapor pressure with TDCP treated foam was estimated as $2.7x10^{-5}$ torr at 25°C. Because TDCP was not detected at 65°C, we used one-half the detection limit for extrapolation. The vapor pressure estimated from TDCP-treated foam was used in the present risk assessment, because it is based on empirical data and it was obtained with TDCP-treated foam. Thus, it replaces two conservative assumptions of the mathematical model, that the FR chemical does not have an affinity for the foam and that the foam does not impede evaporation.

The average daily dose (ADD) for TDCP was estimated to be 0.023 mg/kg-d, with over 99% from inhalation of vapor phase TDCP (Table 12). Because most of the exposure was from inhalation of vapor phase TDCP, the vapor pressure has a significant impact on risk. However, changing the vapor pressure to the highest reported value increases the estimated hazard index and cancer risk only slightly (Table 16). This is because in the standard case, the source strength is near the maximum value allowed by the model. The maximum emission rate is the rate that would deplete all of the FR chemical during the lifetime of the product, defined by equation (7). Changing the vapor pressure to the lowest reported value decreases the hazard index for non-cancer effects to well below a value of one. However, the cancer risk is still greater than one per million, largely due to the contribution of the other exposure routes. Even if the vapor pressure were zero, the estimated risk would be 7 per million (not shown).

Table 16. Effect of Vapor Pressure on TDCP Hazard Index and Cancer Risk [a]

VP, Torr	HI	Cancer Risk per Million	VP Source	Note
$7.4x10^{-8}$	0.05	7	SRC 2006	Estimate
$<1.0x10^{-6}$ [b]	0.08	20	EPA 2005a	Estimate
$2.7x10^{-5}$ [c]	2	300	Bhooshan and Cobb 2005	Empirical, with treated foam
$1.4x10^{-3}$	6	900	Bhooshan and Cobb 2006	Empirical
$1.0x10^{-2}$	6	900	IPCS 1998	Empirical
$2.0x10^{-1}$	6	900	Akzo 1998	Empirical

[a] In adults. VP, vapor pressure; HI, hazard index.

[b] Calculated as one-half the detection limit, or $5x10^{-7}$.

[c] Value used in the risk assessment.

The uncertainty in estimating inhalation exposure can be reduced by obtaining empirical data in a setting that at least approximates typical use. A simple approach would be to measure vapor levels in the impaction studies that were used for particle release. Another approach would be to make measurements in a test house with FR-treated furniture.

In estimating inhalation exposures, the indoor environment was modeled as a two-zone model, including a breathing zone (Thompson and Thompson 1990) and the room in which the upholstered furniture is located. This approach was used because concentrations of airborne pollutants are generally higher near the source. A consumer sitting on a couch is not only close to the source, but the consumer's movements may contribute to it. This breathing zone approach requires assumptions regarding the size of the breathing zone, the air exchange rate between the breathing zone and room air, and the exposure duration in each zone.

An alternative to the two-zone model is a single-zone model in which the zone is the size of an entire home. Any emissions of vapor or particles are assumed to be evenly distributed throughout the home. In reality, the concentrations of airborne pollutants are greater near the source (breathing zone) and in the room where the source is located. However, when interior doors are open or when forced air heating and air conditioning are operating, the differences in concentration are relatively small. Treating the entire home as a single zone essentially averages the various microenvironments (rooms and proximity to the source). Using a one-zone model with a volume equivalent to the room volume (V_2) (120 m^3) would reduce the ADD of TDCP from $9.5x10^{-3}$ mg/kg-d to $5.7x10^{-3}$, or less than 2-fold (not shown). Therefore, in this case the choice of model has a small, perhaps 2-fold, effect on the estimated HI and cancer risk.

Other than the impaction experiments, the potential effects of accelerated aging or wear on dermal or oral exposure were not evaluated. Small-scale mock-ups were used in lieu of furniture samples, which were not available.

C. Variability and Uncertainty

The variability and uncertainty associated with general input parameters were assessed by a sensitivity analysis. That is, the input variables were varied individually from the lower to upper bound. The effects on the estimated exposure were generally modest. In most cases, the estimated exposure varied by less than 5-fold from the best estimate (Tables 13-15). The oral exposure was most sensitive to the hand-to-mouth transfer factor. Changing this parameter to the lower or upper bound changed the oral exposure to either one-tenth or 18-times the best estimate. Dermal exposure was most sensitive to the fabric-to-skin transfer factor, with a range of from one-fifth to 7-fold. Inhalation exposure was most sensitive to the inter-zone air exchange rate. At the lower bound, the estimated exposure increased by almost 5-fold. The effect was minor at the upper bound however.

Furthermore, the sensitivity analysis does not capture all sources of uncertainty. Some parameters are based on data with surrogate chemicals, including the fabric-to-skin and hand-to-mouth transfer factors (Tables 5-11). Hand-to-mouth transfer was used as a surrogate for the fabric-to-mouth transfer factor. Some input parameters, such as the surface area of exposed skin and exposure durations, are based on a combination of empirical data and assumptions. Others, such as the inter-zone air exchange rate and boundary value height, are assumptions. The variability of chemical-specific input parameters, such as migration and particle release, were not considered due to the limited number of samples tested. Thus, variability between different products cannot be assessed.

The primary contributor to the estimated exposure is inhalation of vapor phase FR chemical. However, there are no empirical data to estimate inhalation exposure. Rather, a purely mathematical model was used. Furthermore, this model is highly dependent on the vapor pressure of the chemical. Empirical vapor pressure values are not available for several of the FR chemicals of interest. Their vapor pressures were estimated by mathematical models, in part because the vapor pressures are low and difficult to measure. Nonetheless, we used a mathematical model using input data from another model, compounding the uncertainty. TDCP has measured vapor pressures between 0.01 to 0.24 torr. In contrast, model estimates range from $1x10^{-6}$ torr and $7.4x10^{-8}$ torr at 25°C. The discrepancy between the empirical and estimated vapor pressures suggests that the estimated vapor pressures for PIP and OTB may be highly uncertain.

Probabilistic methods were not used in this case to assess variability and uncertainty, due to the lack of adequate information on the distributions of most of the variables.

Some potentially significant sources of uncertainty are difficult or impossible to quantify. Most of the models and methods used to estimate exposure have not been validated. Thus, it is impossible to know whether these methods reasonably approximate true exposures.

The effect of additional toxicity data on ADI values cannot be predicted. The cancer unit risk estimate for TDCP is highly dependent on the choice of dose response model. At present, it is impossible to know which model is more likely to be correct. The default model used by the CPSC staff generally results in a higher cancer risk estimate. The use of alternative models (e.g.,

non-linear dose response models) would most likely reduce the estimated cancer risk. Using an uncertainty factor approach could result in a negligible cancer risk. However, based on the CPSC chronic hazard guidelines, the default assumption of low-dose linearity is applied unless there is convincing evidence to justify an alternative approach.

While there are many sources of uncertainty, most of them can be addressed by additional studies on toxicity and exposure.

D. Conclusions

The following conclusions are based on limited exposure and/or toxicity data, and should be regarded as preliminary.

Based on a mathematical model derived by the National Research Council (NRC 2000), inhalation of vapor phase FR chemical appears to be the primary route of exposure for TDCP and the components of FM-550™. The model contains several assumptions that may tend to overestimate inhalation exposure. However, the model and certain input parameters are also highly uncertain and, therefore, may either overestimate or underestimate exposure. Empirical data on vapor phase emissions or indoor concentrations are needed to assess whether these chemicals may present a hazard to consumers.

Based on the limited available exposure data, upholstered furniture manufactured with TDCP-treated foam in upholstered furniture might present a hazard to consumers, based on both cancer and non-cancer hazards. As discussed above, empirical data relating to TDCP emissions are needed to assess whether TDCP may be hazardous to consumers.

Based on the limited available toxicity and exposure data, it does not appear that TPP or PIP would present a hazard to consumers. However, there were insufficient toxicity data to derive ADI's for TPP and PIP. This conclusion is based on the assumption that TPP and PIP are not more toxic than other aromatic phosphates. Additional toxicity and exposure data are needed to assess whether TPP or PIP may be hazardous to consumers. The National Toxicology Program (NTP) is considering a request from the CPSC staff to perform additional toxicity studies on aromatic phosphates. The staff will review any additional toxicity data that become available. As discussed above, empirical data relating to emissions of these compounds are also needed to assess whether they may be hazardous to consumers. Exposure data specific for TPP and PIP are also needed to reduce the uncertainty in exposure.

No chronic toxicity data on OTB or related compounds are available. The toxicity and potential risks of OTB cannot be assessed. Basic toxicity data and an empirical vapor pressure (or upper bound) are needed to conduct a preliminary risk assessment for OTB.

Continued development and validation of the exposure methods in general would also serve to reduce the uncertainty in estimating exposure to FR chemicals.

Melamine has been studied in chronic bioassays (reviewed in Thomas and Brundage 2004). Melamine does <u>not</u> satisfy the regulatory definition of toxic. Thus, exposure studies with

melamine-treated foam were not necessary. Based on the available data, melamine-treated foam is not expected to present a hazard to consumers.

A number of other FR treatments that could be used in foam have been discussed by the U.S. EPA's Design for the Environment Program (EPA 2005a).

In summary, the staff concludes that:

- Based on the available data, melamine-treated foam is not expected to present a hazard to consumers.
- Inhalation studies are lacking for TDCP, TPP, PIP, and OTB. This is significant because inhalation appears to contribute the greatest portion of the total exposure.
- Empirical data on vapor phase emissions or indoor concentrations are needed to assess whether TDCP, TPP, PIP, or OTB may present a hazard to consumers.
- Chemical-specific data on liquid-mediation migration and airborne particle release are needed to assess more accurately whether TPP and PIP may present a hazard to consumers.
- Additional toxicity data are needed to derive acceptable daily intake values for TPP and PIP.
- Basic toxicity and physico-chemical data for OTB are needed to derive an acceptable daily intake value and to estimate exposure.

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UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: December 21, 2006

TO : Dale Ray, Project Manager for Upholstered Furniture, Directorate for Economic Analysis

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Michael A. Babich, Ph.D., Chemist, Division of Health Sciences

SUBJECT : Response to Peer Review Comments on the CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam*

The CPSC staff completed a draft risk assessment on the use of flame retardant (FR) chemicals in upholstered furniture foam in January 2006 (Babich et al. 2006). This document was peer-reviewed by two independent experts in toxicology and risk assessment. The staff has made appropriate revisions to the risk assessment (Babich 2006), based on comments from peer reviewers and public comments. Below are the staff responses to the peer reviewers' comments.†

The peer reviewers' comments included the methods and models used to estimate exposure. In particular, the reviewers suggested the use of a "breathing zone" model to estimate inhalation exposure. This resulted in a slight increase in the estimated inhalation exposure. The peer reviewers also requested additional details and discussion. As a result of the changes made in response to the peer review and public comments, the relative contribution of inhalation to total exposure increased. However, the overall conclusions of the risk assessment did not change.

* These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.
† The peer reviewers' responses are reported verbatim.

I. COMMENTS ON EXPOSURE ASSESSMENT

Comment:

"The experimental work presented in the provided documents is excellent and provides some much-needed data. As mentioned in a previous review for FR in mattresses and bedding, these data have been lacking from evaluations of flame-retardant materials conducted to date, and these experimental results are precious in that they represent a significant contribution to the field. Once again we have noted that CPSC staff needs to conduct a painstaking reconstruction and check of all of the algorithm details and calculations that went into the risk assessment. This detailed evaluation of the specific calculations was considered beyond the scope of this peer review, aside from the comments below on a key computational error discovered in all the spreadsheets."

Response:

The CPSC staff has reviewed and verified the calculations.

Comment:

"The most significant issue found in this review was a computational error in the spreadsheets. The calculation of the density of the FR substances measured in the extraction tests drives the estimation of exposure and risk for both the dermal and oral portions of the evaluation. This calculation takes the average amount of FR detected on the 5.5 cm diameter filter paper and calculates a surface density by dividing this amount by the surface area of the filter ($pi*(dia/2)^2$). This calculation is done in cell E24 of the spreadsheets.

The content of cell E24 of all the spreadsheet is: =E19/(PI()*(5.5/2^2))

Microsoft Excel does power or exponentiation calculation before it does division or multiplication within parenthetical expressions. Thus instead of dividing 5.5/2 to calculate the radius and then squaring the result, the 2 in the denominator was squared first and then divided. This resulted in an OVERESTIMATION of **all dermal and oral exposures and risk (HI determinations) of 5.5 fold.**

Thus, all the predicted Hazard Indices will be lower. Those analyses that were driven predominantly by dermal and oral exposure (TDCP and BAE) * with HIs of about 5 or less within this analysis should now correctly have HIs less than 1. The HI for TPP (FM-550) was reduced less (about 2 fold) with the corrections of this error because of the greater contribution of estimated inhalation exposure to overall risk from this FR substance.

Since the dermal and oral routes made up the vast majority of the exposure and risk for TDCP and BAE, correcting this error does not materially change the relative estimated contributions of

* Some of the abbreviations were changed to reflect new information that more specifically identifies certain chemicals. BAE (brominated aryl ester) was changed to OTB (octyl tetrabromobenzoate) and ITP (isopropylated triphenyl phosphate) was changed to PIP (phenol isopropylated phosphate).

these routes. It does materially change the distribution of estimated contributions for TPP (FM-550) taking the inhalation portion of HI from 50% to 85%."

Response:

The expression was inadvertently entered as $\left(\frac{5.5}{2^2}\right)$ instead of $\left(\frac{5.5}{2}\right)^2$. This error was corrected in the revised risk assessment. However, some other changes were made in response to comments from the peer reviewers and public comments. Changes were made to some of the input parameters for estimating dermal exposure, the vapor pressure of TDCP, and the model for estimating inhalation exposure. These changes are discussed in detail below. As a net result of these changes, HI for TDCP is still roughly 1. However, the relative importance of inhalation has increased for TDCP, TPP, and PIP (ITP).

Comment:

"Since the estimated dermal exposure accounts for a majority of the estimated risk for TDCP and BAE, any error or omissions in this analysis will have a significant effect on the overall predictions. The primary manner of estimating systemic absorption in this document was the use of a percutaneous absorption rate combined with other parameters. This assumes that a steady-state has been established between material going onto the skin and then into the circulating elements of the body. This is clearly an overestimating assumption which deserves some discussion in the text especially related to the characteristics of the FR compounds under study."

Response:

The staff agrees that the assumption of steady-state conditions may lead to an overestimation of exposure. We have added this point to our discussion. However, we also note that this approach is protective of public health and is typically used for risk assessment purposes.

Comment:

"Perhaps the largest factor absent from consideration in this analysis is the integration of the effects of standard skin shedding (desquamation) into the estimation of the ultimate absorption of compounds with high values of MW or K_{ow}. Skin is continuously replaced through epidermal turnover, the process by which new cells are generated at the base of the epidermis while the outermost surface flakes off (*i.e.,* desquamates) at the same rate. Of course, any chemical in desquamated skin cannot be absorbed systemically. The typical time required to replace all of the skin cells (birth-to-shedding) in the stratum cornium (sc) is approximately 14 days, but varies with physiological location and age and can be as long as 60 days or shorter than 14 days for diseased skin.

In short, substances that take a relatively long time to penetrate skin will not be absorbed by the body if this up-welling of skin layers occur at a significantly faster rate than the penetration of the toxicant through the sc to the viable dermis. The substance would be shed with the skin cells

and thus eliminated from the body. It would be analogous to a weak or slow salmon that never made it upstream to the "target" pool to spawn but was instead washed back out to sea.

Dr. Wil tenBerge has actually put together a kinetic model of dermal penetration which accounts for the rate of dermal penetration that occurs versus the nominal amount that might be lost via desquamation. This model is available for download at the bottom of the following web page which provides the details of the model: http://home.planet.nl/~wtberge/skinperm.html

Last year, Dr. Annette Bunge shared a preprint entitled: **Does Desquamation Reduce Permeation?** (Micaela B. Reddy and Annette L. Bunge) which I believe confirms the reality and importance of this mechanism for chemicals with high MW (>350 g/mole or high Kow (Kow > 10^4).

Excerpted text from this paper:

> Except for highly lipophilic or large MW chemicals, nearly all of the chemical in the epidermis at the end of an exposure will systemically absorb (i.e., Fraction Absorbed or FA ~ 1), regardless of the length of time the skin was exposed to the chemical. Only for chemicals with large values of MW (> about 350 Da) or logKo/w (> approximately 4 for most chemicals) will epidermal turnover reduce FA significantly.

Clearly, TDCP and BAE fall into this category of MW >350 or logKow >4. While the SKINPERM model could be used to predict the magnitude of this effect, there is arguably not enough data available at this point to specifically quantify this effect on systemic absorption. However, it would be appropriate for the evaluation to include a discussion as explanatory text of the issue of desquamation and its potentially striking implication on dermal exposure and risk."

Response:

Percutaneous absorption of TDCP was measured *in vitro* (Hughes et al. 2001), under an interagency agreement between CPSC and the EPA Human Effects Research Laboratory (HERL). During the planning stages of this work, we sought the advice of Dr. Robert Bronaugh, FDA, who is an expert in percutaneous absorption and has contributed to the development of *in vitro* methods. Because TDCP is hydrophobic, transfer from skin to the receptor medium is expected to be slow, relative to *in vivo* studies. Therefore, we assumed as a reasonable default that any TDCP that reaches the upper, papillary dermis would be absorbed *in vivo*. We agree that this assumption merits additional discussion. We have expanded the discussion on this point in the revised risk assessment.

Comment:

"Oral exposure occurring from hand-to-mouth activity appears to be adequately described by taking the amount of chemical that migrated to the fabric surface from the somewhat superficial wetting/pressure protocol and applying the predicting factors used in the report. The amount of material extracted by direct mouthing or sucking, however, may not be reasonably simulated by using the amount of chemical that migrates to the fabric surface in this test.

Two factors could combine to exacerbate the oral exposure from sucking. First, the volume of saliva injected into and potentially sucked out of the foam by a child could be anticipated to be much greater than the amount used in the migration protocol. Second, this added volume of warm "extractant" would be expected to penetrate more deeply into the foam and thus potentially be able to pull out more FR substance from it per active sucking event and unit area.

A simple protocol to gauge this exposure potential would be to saturate a small (ca. 3 cm x 3 cm x 1 cm thick) section of foam with approximately 10 cm^3 of saline initially at 36-38°C in a small watch glass or dish. After wetting, knead the wetted foam for 10 minutes, squeeze to express the water from the foam, analyze the extractant and estimate the amount per cm^2 extracted. One could then use this value for M in equation 3. Please note: that M for hand-to-mouth transfer would continue to use the current migration data and these experimental values would also be used in equations 1 and 2. If a different protocol results in a different values of M for direct mouthing – it should have a different notation to differentiate it from transfer, perhaps M_m for direct mouthing transfer and M_t for hand-to-mouth transfer. This would also mean that equation 4 would need to be reconstructed to account for these two types of M values.

The above protocol is only one suggested approach. The point is that the amount of FR obtained from the current migration procedure is most likely not representative of that obtainable during the direct mouthing/sucking scenario and that a more rigorous extraction test is needed to simulate this potentially critical exposure route."

Response:

In prior work, the CPSC staff has used several methods to estimate oral exposure due to migration of chemicals from various substrates. We have considered the comments presented here. However, the staff concludes that the CPSC staff method of measuring leaching, which involves a significant volume of liquid and a weight, is sufficiently stringent to estimate oral exposure in children. Furthermore, in observational studies conducted by the CPSC staff, direct mouthing of furniture by children was an infrequent event (Kiss 2002; Smith and Kiss 1998).

Comment:

"Inhalation exposure represents a relatively small portion of the overall predicted exposure for TDCP and BAE but represents a significant portion of the exposure predicted for TPP (FM-550). There are a number of issues related to this estimate in the report that are worthy of mention. While these comments and suggested actions would most likely not provide results that would change the conclusions of the report for TDCP and BAE, they could change the results of the estimated exposure to TPP (FM-550).

The only experimental measurement related to inhalation exposure in the report occurred for the determination of particulate emission during normal use. The protocol used is quite ingenious. and does indeed show that the level of exposure from airborne particulate is extremely low relative to any reasonable exposure limit (*i.e.*, truly de minimus).

Unfortunately, there is no experimental determination of C_{sat}, only its estimation from VP (cited for TPP and model-estimated for TDCP and BAE). C_{sat} in turn drives the estimation of source strength, which is used to calculate breathing zone concentrations. This approach introduces a considerable amount of uncertainty which could be reduced by the direct measurement of C_{sat}.

The value for VP for TDCP and BAE is estimated in the report at ½ the estimated upper bound figure or 5×10^{-7} torr. This vapor pressure would render a C_{sat} of:

$$Csat = \left[\frac{5x10^{-7}}{760}\right] * (10^6) = 6.6 \times 10^{-4} \text{ ppm v/v}$$

C_{sat} TDCP = 0.012 mg/m^3
C_{sat} TPP/ITP = 0.110 mg/m3 (based on VP = 6.3×10^{-6})
C_{sat} BAE = 0.015 mg/m^3

Note: The following relationship was used to convert ppm v/v to mg/m^3.

$$\frac{mg}{m^3} = \left[\frac{MW}{24.4}\right] * ppmv/v$$

It is suggested that a relative simple laboratory protocol could be used to significantly refine these estimates. This would be done by first taking 6 square pieces of 1 m^2 foam joined to form a 1 m^3 cubic box and then allowing the interior volume of this closed foam box to equilibrate at room temperature. Given enough time, the offgassing FR substance will equilibrate at C_{sat} in the box without the effect of absorptive losses to any non-ventilatory surface sinks.

Consider a volume with an initial fixed level of airborne concentration ($C_0 = 100$) and no new material entering the room air with the incoming ventilation. Given good mixing, this situation is described as:

$C = C_0 e^{-(\text{ventilation rate/volume})(\text{time})}$

C= concentration in the room at any time
C_0 = concentration in the room at time = 0
ventilation rate = volume/time

When the product of (ventilation rate) and (time) equals the chamber volume, a single mixing air change has occurred and $C = C_0 e^{-1}$ or $C/C_0 = .368$. In this situation C would be reduced from 100 to 36.8 after a single air change and approximately 63% of the original molecules (air and contaminant) were removed.

Thus, it can be shown with first principle kinetic modeling that any volume of contaminated air that is replaced with good mixing with an equal volume of incoming pure air (i.e., 1 m^3 of air into a 1m^3 box) will lose 63% of the original air (and contaminant) molecules and retain 37% of the original air and contaminant. Thus, a 1 m^3 air sample taken from the interior volume of this

box should capture at least 63% of the FR molecules originally in the box air with approximately 33% remaining in the box due to the influx and mixing of make up air that would occur during air sampling. Assuming all of the above estimated vapor pressures are correct, this would mean the collection of an analytical sample amount of 8 micrograms of TDCP and 9 micrograms of BAE. Doing the same analysis with TPP/ITP should yield a sample of about 69 micrograms. Thus the determination of C_{sat} for each FR substance out of the foam box would simply be the sampled concentration divided by 0.63. Note that this analysis also assumes that there are no new emissions to the air volume during the relatively short sampling period.

Indeed, given the excellent laboratory capabilities demonstrated by the CPSC, analytical detection limits in the fraction of a microgram range could dramatically drive down the determined C_{sat} for any and all of the compounds out of real foam. For example, assume that BAE was a "non-detect" at a limit of detection (LOD) <0.5 ug. Since the estimated C_{sat} predicts 9 ug of BAE, a "non-detect" at LOD <0.5 ug would lower the determined C_{sat} (and subsequently the estimated exposure) by approximately 18 fold versus the current estimate.

C_{sat} is a critical value for the estimation of inhalation potential; however, the length of time it takes to reach a significant portion of this saturated concentration could also be an important factor especially as it relates to bolus injection of vapors into room air from foam contraction which will be discussed below. Once the time-to-equilibrium is established at room temperature, conducting the tests at 45°, 35° and 25° C would dramatically enhance the amount of available analytical sample and improve our understanding of just how much FR is potentially coming off as a vapor into real rooms."

Response:

The reviewer provided a helpful discussion on the importance of C_{sat} in estimating inhalation exposure to vapor phase FR chemicals.

For a pure compound, C_{sat} should equal the theoretical value estimated from the vapor pressure, provided that the temperature and atmospheric pressure are the same. For FR-treated foam, an empirically determined C_{sat} may be lower due to interactions between the FR and the foam. Using an empirical or "effective" C_{sat} measured with treated foam would be slightly more accurate. However, even with an empirical C_{sat}, there would still be considerable uncertainty in estimating inhalation exposure, because the source strength was estimated by means of a theoretical model, rather than measuring it in a chamber or test house.

In revising the risk assessment, we estimated the "effective" vapor pressure of TDCP using TDCP-treated foam (Cobb and Bhooshan 2005). We used this value (2.7×10^{-5} torr) to estimate inhalation exposure in the revised risk assessment. In addition, we more thoroughly investigated the available data on the vapor pressure of pure TDCP (Babich 2006). We found empirical and estimated values from authoritative sources (EPA, National Library of Medicine, International Programme on Chemical Safety, and industry reports) that ranged over seven orders of magnitude (7.4×10^{-8} to 0.2 torr). The "effective" vapor pressure from TDCP-treated foam was much greater than the value we used in the draft risk assessment (5×10^{-7} torr), although it is less than empirical values for pure TDCP (0.0014 to 0.2 torr).

In response to comments from peer reviewers and others, the staff made a number of changes in the input parameters and models used to estimate exposure. As a result of these changes, the estimated dermal exposures were generally lower, while the estimated inhalation exposures generally increased. Therefore, the relative contribution of vapor phase inhalation has greatly increased.

Comment:

"Other areas of the analysis that could be improved include the determination of the affected volume for emissions from foam furniture and the determination of the diffusivity (D_{air} or D_{ab}) of FR compounds in air. Finally the topic of bolus injection of vapors into room air from rapid foam contraction (sitting) will be discussed separately below.

The current methodology estimates the source term for release of particles from a small-volume (glove box) experiment and then scales that source term into a much larger well-mixed single box (320 m^3) room/house model. As mentioned in our previous review, the exposure scenario suggested by these particle emissions can be reasonably described using the following characteristics:

- Relatively small emission area in a relatively large room and house volume,
- impaction source proximate to the breathing zone of the subject (i.e., the subject is causing the emission and persona cloud, and
- the potential for relatively large and quickly settling particles

All of the above suggests that the well-mixed room or house volume model will dramatically under-estimate the breathing zone concentration of particles resulting from this essentially "near-field" or proximate source. It would be more appropriate to take the airborne concentration in the smaller volume of the glove bag as a reasonable approximation of the "near-field" concentration around the breathing zone of the person in bed. Going from 320 m^3 for the whole house volume to 1 m^3 as a personal cloud volume represents two to three order of magnitude increase in exposure. Values for potential inhalation exposure from particulate are so small, however, as to still be *de minimus*, even with this increase."

Response:

As discussed in the risk assessment, we considered two approaches. One approach is to consider exposure in the room where the furniture is located, which requires assumptions for consumer activity patterns, that is, the amount of time spent in each room. We chose a simpler approach, which was essentially to "average" the exposure over the entire home for 16 h, the average time that a consumer spends at home. Thus, the increased concentration in the room where the source is located, in the first approach, would be off-set by the shorter exposure duration in the second approach.

Nonetheless, we agree that our approach could significantly underestimate exposure to particulate and vapor emissions. As suggested by the reviewer, we used a third approach to

estimate inhalation exposure in the revised risk assessment. In this approach, a consumer sitting on the furniture is considered to be in a "breathing zone," that is, a location that is intimately associated with the source of emission. The breathing zone exchanges air rapidly with the remainder of the room. This change increased the estimated inhalation exposure by less than 2-fold.

Comment:

"There is also a strong likelihood that exposure from FR vapors is relatively low and this is particularly true for emissions from TDCP and BAE. In light of the above mentioned imprecision in the likely overestimation of C_{sat} vapor concentrations and vapor emission source rates we believe that an uncertainty analysis with the primary diffusion of vapors into smaller affected volumes would be appropriate. This analysis could help to inform a decision on whether to do actually testing of C_{sat} especially for TPP (FM-550)."

Response:

As discussed above, the staff made a number of changes in the input parameters and models used to estimate exposure in response to comments from peer reviewers and others. As a result of these changes, the estimated dermal exposures were generally lower, while the estimated inhalation exposures generally increased. Therefore, the relative contribution of vapor phase inhalation has greatly increased.

Comment:

"The molecular diffusivity in air (D_{air}) calculated for the FR substances used a referenced relationship from Schwope *et al* 1989. A more refined algorithm to estimate D_{air} has actually been developed and published more recently by the EPA. Specifically, this includes the evaporative source term algorithms from a subsequent publication of the US Environmental Protection Agency (EPA 1991 Engineering Manual [EPA (1991). Preparation of Engineering Assessments, Volume I: CEB Manual, Chemical Engineering Branch, Economics and Technology Division, Office of Toxic Substances, Washington, D.C. February 28, 1991. pp. 4-23 to 4-33] were used. The key equations in this document for emission from vaporizing pools are presented below along with their designations within this reference:

$$G = \frac{13.3792\, M\, P^{\bullet}\, A}{T} \left(\frac{D_{ab}\, V_z}{\Delta Z} \right)^{0.5}$$

Equation 4-22

where:
- G = Generation rate, lb/hr
- M = Molecular weight, lb/lb mole
- $P^{\bullet}$ = Vapor Pressure, inches of Hg
- A = Area, ft^2

D_{ab} = Diffusion coefficient, ft^2/sec of compound a through b (in this case b is air) – the same as D_{air}.
V_z = Air velocity, ft/min
T = Temperature, °K
Δz = Pool length along flow direction, ft

Gas diffusivities of volatile compounds in air are available for several existing chemicals. However, the diffusion coefficient often will not be known. An equation to estimate diffusion coefficient is expressed as:

$$D_{ab} = \frac{4.09\,x\,10^{-5}(T)^{1.9}\left(\frac{1}{29}+\frac{1}{M}\right)^{0.5}(M)^{-0.33}}{P_t}$$ **Equation 4-23**

where: D_{ab} = Diffusion coefficient, cm^2/sec
(NB : the units of D_{ab} are different in Equations 4-22 and 4-23)
T = Temperature, °K
M = Molecular weight, lb/lb mole
P_t = Pressure, atm

Equation 4-23 is arguably more refined than equation 10 in the evaluation.

Converting D_{ab} in Equation 4.23 to units of ft^2/sec and substituting:

$$G = \frac{2.79\,x\,10^{-3}\,M^{0.835}\,P^{\bullet}\left(\frac{1}{29}+\frac{1}{M}\right)^{0.25}\left(V_z\right)^{0.5}\,A}{T^{0.05}\Delta z^{0.5}P_t^{0.5}}$$ **Equation 4-24**

where: G = Generation rate, lb/hr
M = Molecular weight, lb/lb mole
$P^{\bullet}$ = Vapor Pressure, in. Hg
V_z = Air velocity, ft/min
A = Area, ft^2
T = Temperature, °K
Δz = Pool length along flow direction, ft
Pt = Overall pressure, atm

One could use any C_{sat} determined experimentally as suggested above to directly calculate the effective vapor pressure, $P^{\bullet}$, using a rearrangement of equation (9) of the CPSC report. Given a value for $P^{\bullet}$ the above equation could be used to estimate or gain some insight into the time required to achieve equilibrium in any enclosed volume."

Response:

The CPSC staff could consider using a different algorithm for estimating D_{air} or the source strength. However, the exposure from vapor phase inhalation is based on a theoretical model. A different algorithm would not address the many other uncertainties in the exposure estimate. Due to its relative importance to overall exposure, it is more important to obtain empirical data to estimate inhalation exposure.

Comment:

"Bolus Injection of Vapors Into Room Air from Foam Contraction

[*While working on another project, one of our colleagues*] suggested the following inhalation exposure scenario for FR treated foam:

"Given enough time, the FR compound will vaporize into the void volume of the foam ultimately to a concentration of C_{sat} for that compound coming out of that polymeric matrix. When the foam is contracted (from someone sitting on it) the amount of FR substance potentially injected into the surrounding air would be equal to (C_{sat}) x (Compressed Volume). This direct injection mechanism could conceivable result in relatively high localized breathing zone concentrations of the FR substance around the contracted area.

The appropriate gauging of this effect would require the estimation of both C_{sat} and the compressed volume. One would also need to understand the kinetics of vaporization to determine the time course and capacity of this effect. If the vaporization rate is relatively slow, then this effect would not contribute significantly to the indoor concentrations or the exposure potential.

Given a more accurate estimation of C_{sat} and the emission rate of FR vaporization to air from foam, our opinion is that it is highly unlikely that the bolus injection from foam contraction would provide a significant level of exposure for the current FR substances of interest. However, our opinion is not a risk assessment. Conformation of that opinion means first conducting a reasonable worst-case uncertainty analysis of this factor with the current uncertain (but likely over-estimated) estimates of C_{sat}. Reasonable worst case estimates of compressed volumes, rates of sitting, and an assumption of quick "recharge" of the FR concentration in the void volume could also dramatically overestimate the exposure and risk from this mechanism. If this analysis indicated an HI significantly greater than 1, then refined estimates for C_{sat} and FR vaporization rate might be necessary."

Response:

As discussed by the reviewer, the importance of this pathway depends on the rate at which vapor phase FR chemical in the cells of the foam is replenished. Given the surface to volume ratio, this might occur rapidly. One way to assess this would be to measure vapor phase FR during the impaction tests. We added a discussion of this model to the revised risk assessment.

We performed some simulations to gauge the relative contribution of an "injection" model to inhalation exposure. Such a model requires several assumptions, such as how frequently and to what depth the foam is compressed. The depth of foam compression would depend on the foam properties, weight of the consumer, and velocity of motion. These assumptions, which are difficult to verify or measure, make the model highly uncertain. We estimated that the vapor phase inhalation exposure from the injection model is about 40% of that from the NRC model.

Comment:

"<u>Uncertainty Analysis</u>

We commend CPSC for conducting a sensitivity analysis for the exposure parameters. While it can be more informative to vary multiple parameters simultaneously, the approach used by CPSC gives reasonable estimates of the impact of uncertainty in the input parameters and the magnitude of a reasonable upper bound estimate of exposure. CPSC also provided practical and level-headed interpretations of the results of the sensitivity analysis. Aside from the additional analyses suggested above, we have no comments on the sensitivity analysis or discussion of uncertainty."

Response:

We chose to perform a sensitivity analysis for exposure parameters, rather than a probabilistic analysis, because only limited information was available on the distributions of the input parameters. We consider that a probabilistic analysis with such limited data could provide the reader with a false sense that the uncertainty and variability in this risk assessment are well-characterized.

II. COMMENTS ON TOXICITY AND DOSE-RESPONSE ASSESSMENT

Comment:

"While it is recognized that CPSC is an independent agency, CPSC may wish to consider further harmonization with the methods of other organizations*. This includes the use of benchmark dose methods, inhalation dosimetry for effects on the respiratory tract, consideration of the implication of extrapolation from subchronic to lifetime exposures, and the use of chemical-specific adjustment factors instead of uncertainty factors. Other agencies and organizations, including the Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, and the International Programme on Chemical Safety (IPCS) include some or all of these considerations. For example, Health Canada includes an uncertainty factor of 1-100 for inadequacies of the database, including lack of adequate data on developmental, chronic or reproductive toxicity, use of a LOAEL, and inadequacies of the critical study (Meek et al., 1994). While these specific adjustments may not always have a significant impact on the overall assessment, use of these values, where possible and feasible within resource limitations, tends to improve the scientific basis for the assessment.

In this spirit of harmonization, Table 1† presents risk values for the FR chemicals developed by other organizations and the bases for these values. The data are from the NAS review of flame retardants (NRC, 2000), and IRIS data from EPA (http://www.epa.gov/iris/), and supplemented by data from ATSDR. Key differences from other organizations are bolded. The ITER database (available at http://www.tera.org/iter/ and http://toxnet.nlm.nih.gov/) provides key information about risk values developed by U.S. and international agencies, as well as independently-developed and peer-reviewed values, and can be a resource for such information."

Response:

The risk assessment, including the use of uncertainty factors, was conducted according to the CPSC Chronic Hazard Guidelines, which were issued in 1992. The guidelines do not provide for additional uncertainty factors to account for inadequacies of the data base or for the potential sensitivity of children relative to adults. However, the guidelines allow the use of chemical-specific adjustment factors on a case-by-case basis, provided there are sufficient data to deviate from the default factors. In the present case, the CPSC staff did not consider that there were adequate data to justify the use of chemical-specific uncertainty factors. The differences

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* "Note that harmonization is not standardization. Harmonization involves (1) understanding the methods and practices used by various organizations; (2) developing confidence in, and acceptance of, assessments using different approaches; and (3) willingness to work toward a convergence of methodologies as a long-term goal (Sonich-Mullin, 1997)."

† Table 1, provided by the peer reviewers, appears on page 14 of this document.

Table 1. Comparison of Toxicity Values of FR Chemicals Developed by Various Organizations*

Chemical	CPSC	NAS	EPA	ATSDR
Tris (1,3-Dichloro-2-Propyl) Phosphate (TDCP)	ADI = 0.005 mg/kg-day LOAEL = 5 mg/kg-day (Biodynamics 1981) UF = 1000 (10A, 10H, 10L) Oral cancer unit risk = 0.031/mg/kg-day (based on q1 from BMD modeling for kidney and liver tumors combined) Date: 2006	RfD = 0.005 mg/kg-day LOAEL = 5 mg/kg-day (Biodynamics 1981) UF = 1000 (10A, 3H, 10L, 3D) RfC = 0.018 mg/m^3 (based on route-to-route extrapolation from RfD) Oral unit risk = 0.06 /mg/kg-day (based on BMDL extrapolation to zero for testicular tumors) Inhalation unit risk = 1.71 x 10^{-5}/ug/m^3 (based on route-to-route extrapolation from oral unit risk) Date: 2000	No RfD/RfC	No assessment
Triphenyl Phosphate (TPP)	Possibly toxic in humans. Insufficient information to derive an ADI directly. NOAEL = 160 mg/kg-day (Sobotka et al., 1986)	No assessment	No RfD/RfC	No assessment
Isopropylated Triaryl Phosphate (ITP)	Possibly toxic in humans. Insufficient information to derive an ADI	No assessment	No RfD/RfC	No assessment
Brominated Aryl Esters (BAE's)	Insufficient information to determine whether the BAE's are "toxic" in humans or to derive an ADI.	No assessment		
Tris (1,3-Dichloro-2-Propyl) Phosphate (TDCP)	ADI = 0.005 mg/kg-day LOAEL = 5 mg/kg-day (Biodynamics 1981) UF = 1000 (10A, 10H, 10L) Oral cancer unit risk = 0.031/mg/kg-day (based on q1 from BMD modeling for kidney and liver tumors combined) Date: 2006	RfD = 0.005 mg/kg-day LOAEL = 5 mg/kg-day (Biodynamics 1981) UF = 1000 (10A, 3H, 10L, 3D) RfC = 0.018 mg/m^3 (based on route-to-route extrapolation from RfD) Oral unit risk = 0.06 /mg/kg-day (based on BMDL extrapolation to zero for testicular tumors) Inhalation unit risk = 1.71 x 10^{-5}/ug/m^3 (based on route-to-route extrapolation	No RfD/RfC	No assessment

* Table provided by the peer reviewers.

Chemical	CPSC	NAS	EPA	ATSDR
		from oral unit risk) Date: 2000		
Triphenyl Phosphate (TPP)	Possibly toxic in humans. Insufficient information to derive an ADI directly. NOAEL = 160 mg/kg-day (Sobotka et al., 1986)	No assessment	No RfD/RfC	No assessment
Isopropylated Triaryl Phosphate (ITP)	Possibly toxic in humans. Insufficient information to derive an ADI	No assessment	No RfD/RfC	No assessment
Brominated Aryl Esters (BAE's)	Insufficient information to determine whether the BAE's are "toxic" in humans or to derive an ADI.	No assessment	No RfD/RfC	No assessment

between CPSC's risk assessment practices and those of other U.S. agencies are minor and have been discussed elsewhere in detail (Babich 1998; Rhomberg 1997).

Comment:

"It would be useful for the documentation in the quantitative assessment to provide sufficient rationale for the readers to understand the reasons for the key decision points, particularly where CPSC decisions differed from those of other organizations. While the reader can be referred to the qualitative assessment for additional details (where such details are provided in that assessment), it can be useful to have all of the key exposure *and* toxicity decisions documented in one place. It would be desirable for each chemical summary to include an overall picture of available database, even in light of the brief summary in the risk assessment document. For example, although the two-year chronic study for TDCP was judged to be the critical study, the findings from this study are supported by other studies, such as acute and subchronic studies, developmental and reproductive studies, and neurotoxicity studies. The current version of the summary document (risk assessment document) does not mention the existing developmental and reproductive studies, probably due to the lack of positive findings from these studies. Without such supporting information, the confidence for the derived ADIs would be significantly compromised. The differences in the methods used by different regulatory agencies in risk assessment highlight the importance of clear documentation of the key decision points in deriving risk values." {see Table 1}

Response:

The staff agrees with the reviewer, and has substantially expanded the summaries in the hazard identification and dose response sections in the revised risk assessment.

Comment:

"The summary document does not mention any information about potential skin and eye irritation effect. In addition, there was no mention of any information about inhalation toxicity. Since such data may be available, it would be helpful to briefly mention the results even though they showed negative responses."

Response:

This information has been added to the hazard identification section of the risk assessment.

Comments on Specific Chemical Assessments

"These comments are based on review of the qualitative and quantitative assessments for the chemicals of interest provided by CPSC, supplemented by other documentation provided by authoritative reviews by other organizations or agencies. Since TDCP is the only one among the four chemicals summarized in the CPSC review document that has enough data for deriving an ADI, a more detailed discussion is provided for TDCP."

Comment:

Tris(1,3-Dichloro-2-Propyl) Phosphate (TDCP)

"We recognize that the purpose of the primary document being reviewed (the risk assessment document) is to focus on the overall risk assessment, rather than the details of the studies. However, as mentioned in the general comments, it is much easier for the reader, and improves the overall credibility of the assessment, if the key toxicity information is presented. While it is appropriate to reference the supporting documents for the study details, it is recommended that CPSC include a list (either text or tabular) of other relevant studies (including the neurotoxicity, developmental, and reproductive toxicity studies). It would be useful for this list to identify the effects observed and NOAELs/LOAELs. For example, neurological effects were mentioned in the summary of acute studies, but the risk assessment document did not address the follow-up neurotoxicity studies conducted in hens treated with repeated doses of TDCP (Stauffer Chemical Co., 1981; Celanese Corp., 1960). Description of the findings from these latter studies would present a complete picture of the potential neurotoxicity of TDCP. In addition to data on toxicity from oral exposure, the summary should also include information on available toxicity information from dermal and inhalation exposure. At the least, it would be useful to note that few data are available for these routes. In addition, as noted below, it would be useful for CPSC to do some rough analyses to evaluate the importance (or lack thereof) of these data gaps."

Response:

Additional information has been added to the hazard identification, dose response, and discussion sections.

Comment:

"As an important component of hazard characterization, information regarding reproductive and development toxicity should always be mentioned. Even though the detailed information is presented in the earlier supporting documents, summarizing the results of the reproductive and developmental toxicity studies in the risk assessment document would address a potential data gap in the reader's mind, even if these studies show negative results (e.g., for TDCP, developmental toxicity only in the presence of maternal toxicity or no reproductive effects in rabbits). Three developmental and reproductive studies have been conducted in two different animal species, rabbit and rat (Wilczynski et al., 1983; Stauffer Chemical Co., 1977-1978; Kawashima et al., 1983; Akzo Nobel Functional Chemicals LLC, 2001). Results of these studies are of particular relevance for TDCP, since the critical effect for the noncancer assessment is a male reproductive endpoint. It would be useful to address consistency between the negative results in these studies and the use of a male reproductive effect as the critical effect. We agree that this inconsistency is not necessarily problematic, since the two-year bioassay was in rats and the male reproductive toxicity study was in rabbits, and different endpoints were evaluated, but these differences should be noted. Overall, further consideration of endpoints evaluated and relative sensitivity of the species would be useful, since the rabbit NOAEL of 200 mg/kg-day for male reproductive function was 40x the rat *LOAEL* of 5 mg/kg-day."

Response:

Additional explanation has been provided.

Comment:

"It would be useful to state more explicitly in the risk assessment document what the experimental protocol was for the chronic two-year study in rats (e.g. "animals were exposed... in diet for 2 years). Because this document only mentions the interim sacrifice, but does not mention the terminal sacrifice, the reader may wonder whether the dosing in this study continued for two years or just one year followed by a 12-month recovery. The text could also be clarified if the terminal sacrifice and number were noted after the mention of the interim sacrifice. More significantly, it is not clear from the text whether the reported effects were observed at the interim or terminal sacrifice, and whether there was any progression with additional exposure. In addition, the identification of doses tested should include the dose of 0 mg/kg-day, to make it clear that the study did include the appropriate control.

Although the summary identifies the lowest treatment dose of 5 mg/kg-day as a free-standing LOAEL, it does not identify the effects on which this judgment was based. It would be useful to remind the reader that the LOAEL is based on seminal vesicle lesions, and to more specifically identify the observed lesion(s)."

Response:

Additional information has been included in the revised risk assessment.

Comment:

"While it appears that the focus of the genotoxicity summary is strictly in support of the carcinogenicity assessment, it would be useful to provide some additional information. In particular, more information and/or further analyses would be useful regarding the "mixed results" in mammalian systems. Were consistent results observed within a study type (e.g., DNA damage, gene mutation, chromosome aberration)? The more detailed evaluation by CPSC in Ferrante (1999b), describes "weak or variable" results in mammalian systems. It would have been useful to provide more information in that document regarding the "variable" results, and interpretation of those studies. In particular, it was not clear whether Ferrante (1999b) considered all of the relevant studies evaluated by NRC (2000). Ferrante (1999b) also presented a nice review of studies investigating different microsome activation systems. However, it would have been useful for CPSC to conduct a more critical evaluation of the overall conclusion regarding the impact of the S9 systems, such considerations may provide information regarding the enzymes that metabolize TDCP to a genotoxic form. Regardless of the conclusions of this analysis of the impact of S9, a brief statement should be included in the final risk assessment, noting the variety of S9 systems tested and the results and implications of such testing.

Most of the tumor response data showed a dose-response trend. Nevertheless, adenomas of the adrenal cortex were significantly elevated only in mid-dose males and were reduced in mid-dose

females, with no significant changes in the high dose groups. These observations raise an issue about whether the increase in this tumor observed in mid-dose animals was chemical treatment-related, and if so, whether it was biologically significant. Adding an analysis of these considerations would facilitate the reader's understanding of the significance of these observations."

Response:

Additional information was included in the hazard identification and discussion sections of the revised risk assessment.

Dose-response assessment

Comment:

"As stated in the general comments, it would be useful for the documentation in the quantitative assessment to provide sufficient rationale for the readers to understand the reasons for the key decision points, particularly where CPSC decisions differed from those of other organizations. For example, in noncancer assessment, a composite uncertainty factor of 1000 was used to account for interspecies and intraspecies differences, and for LOAEL to NOAEL extrapolation. However, NRC used an uncertainty factor of 1000 to account for interspecies and intraspecies differences, LOAEL to NOAEL extrapolation, and database deficiency. Thus, although both organizations calculated the same final value, the approach used (and presumable the rationale used), differed. It would be useful for CPSC to present the rationale for the uncertainty factors in a bit more detail, explaining how and why its values differ from those of NRC."

Response:

Additional explanation was included in the dose response section of the revised risk assessment.

The CPSC staff applied an overall uncertainty factor of 1,000 to the LOAEL, including 10-fold for animal to human extrapolation, 10-fold for inter-individual variability, and 10-fold because a no-observed-adverse-effect level (NOAEL) was not established. This results in an ADI level of 0.005 mg/kg-d. These are the default uncertainty factors described in the CPSC chronic hazard guidelines (CPSC 1992).

The NRC subcommittee derived a reference dose (RfD)* of 0.005 mg/kg-d (NRC 2000). However, the NRC subcommittee applied uncertainty factors of 10-fold for animal to human extrapolation, 3-fold for inter-individual variability, 10-fold because a NOAEL was not established, and 3-fold for an incomplete database. The CPSC chronic hazard guidelines do not provide for an additional uncertainty factor for an incomplete database (CPSC 1992). The default factor for inter-individual variability used by the CPSC staff and others is 10-fold. The NRC subcommittee applied a 3-fold factor for inter-individual variability in this case, because

* Both the acceptable daily intake (ADI) and reference dose (RfD) are estimates of the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects.

there was no evidence of increased sensitivity of juvenile animals from developmental toxicity studies (NRC 2000). They did not indicate what studies were lacking from the database.

Comment:

"The summary document states that benign tumors of the testes and adrenal cortex were not included in the calculation of cancer unit risk, but the summary provides no rationale why these endpoints were not used. The rationale for this decision should be presented."

Response:

Additional explanation was included in the dose response section of the revised risk assessment.

Benign tumors of the testes and adrenal cortex were not included, because no malignancies were present in the organ sites. Thus, it does not appear that these particular tumors would progress to malignancy. In addition, testicular interstitial cell adenomas have a high background rate in rats, and their relevance to human cancer risk is uncertain (CPSC 1992, p. 46636).

Comment:

"The CPSC approach of combining incidence data for males and females when the separately-computed unit risks differ by less than a factor of two is a reasonable approach in general, although it is not identical to the approach of other international regulatory agencies. However, the approach of calculating the human equivalent dose (HED) when data are combined should be considered further. Because the body weight to the ¾ conversion is designed to adjust for differences in tissue dose between species, it seems that a preferred approach for combining risk would be to calculate the risk for each sex separately, calculate the HED, and then combine risk, rather than incidence. This accounts (at least roughly – considering scaling but not sex-specific differences in enzyme expression) for sex-specific differences in tissue dose for a given mg/kg-day (which could affect the resulting tumor incidence), as well as accounting for differences in background response."

Response:

In this particular case, both the background tumor levels and dose-dependent tumor incidences were roughly similar. The alternative approach of calculating sex-specific unit risks separately and then averaging them would have a negligible effect.

Comment:

"Using the maximum likelihood estimate of extra risk (q1) as the basis for the unit risk is a reasonable choice that is consistent with the approach used by some organizations, but different from that used by others. However, CPSC should explicitly note this decision in the section on risk calculations (comparison to exposure), in addition to the current identification of this choice in the dose-response assessment. Consideration of bounds could also provide useful input to the nice uncertainty discussion in the document. While the software used by CPSC does not

calculate the lower confidence limit for the estimated q1 (i.e., the q1*), other software can do so. Alternatively, CPSC could use the approach used by the USEPA, calculating the BMDL10, and then using linear extrapolation to zero. While comparing these results with that using the q1 would not capture all of the uncertainties relating to cancer risk, the comparison would capture at least some of the uncertainties related to model choice and experimental variability."

Response:

The staff has added a discussion of the effect of model choice to the discussion section of the revised risk assessment.

The risk assessment was conducted in accordance with the CPSC chronic hazard guidelines. The software used by the CPSC staff does, in fact, calculate q_1*. We use q_1* when q_1 is zero to ensure a linear dose response. The uncertainty in the estimate of q_1 (generally within 3-fold) is small in comparison to the uncertainty associated with the choice of mathematical model.

The current EPA approach—benchmark dose combined with linear extrapolation—would give a unit risk that is very similar to that calculated by the CPSC staff. The primary difference is that the CPSC staff prefers to use the best estimate of risk, rather than the upper confidence limit. The use of a non-linear model, however, would result in a much lower estimate of risk.

Comment:

"It would be helpful if the mathematical equation for calculation of the unit risk for humans from the rat data (based on the unit risk is proportional to body weight to the three-quarters power) were presented. While this calculation is fairly standard, presentation of the equation enhances transparency, especially since some aspects of the conversion can lead to confusion."

Response:

The equation was added to the dose-response section.

Comment:

"Another method used in the dose-response analysis that is different from that used by other agencies is the addition of unit risks for different endpoints (liver and renal tumors). Again, while cogent arguments can be made for this approach, it would be useful to provide additional information regarding its rationale."

Response:

The risk assessment was performed in accordance with the CPSC chronic hazard guidelines. The differences between CPSC staff's risk assessment practices and those of other U.S. agencies are minor and have been discussed elsewhere in detail (Babich 1998; Rhomberg 1997).

The cancer risks for different tumor sites are calculated separately, because they are considered to arise independently. This practice could result in a slightly greater unit risk, relative to using total tumor incidence, if there are individual animals in the bioassay with tumors at both sites.

Comment:

"Although there are only very limited data from inhalation studies, a robust database from oral exposure studies could provide valuable information for deriving inhalation ADI. Since TDCP is not water soluble, and not a reactive compound, it is expected to produce similar systemic toxicity as by oral route exposure. This means that the approach used by CPSC in the calculation of risk (using only the systemic dose rather than considering portal of entry effects from inhalation exposure) is appropriate as an initial calculation. However, it should be noted that chemicals absorbed from the gastrointestinal tract have to go through first-pass metabolism before they reach the systemic circulation, while parent compound absorbed from the respiratory tract can be directly distributed throughout the body before it is metabolized. Therefore, route-to-route extrapolation from oral data to inhalation exposure needs to present any available information regarding the potential impact of first-pass metabolism on effects or on internal dose. In particular, it would be useful for CPSC to further consider whether the noncancer toxicity of TDCP is due to the parent compound or to a metabolite. First-pass metabolism would decrease the tissue dose (for the reproductive tract, but not necessarily for the liver) of the parent compound from the oral route, compared to the tissue dose of the parent from inhalation exposure to the same amount. This means that a given "dose" from inhalation exposure may have greater toxicological consequences than the same dose from oral exposure. Conversely, inhalation exposure may result in lower tissue doses to a metabolite than the "equivalent" oral exposure, again depending on the target and mode of action. Further consideration of this issue by CPSC would be important. In addition, the discussion of uncertainty should capture this issue, since it could result in inhalation exposure contributing a different, and possibly higher, percentage of total dose than is apparent from Table 4."

Response:

A discussion of the reviewer's points has been included in the discussion section of the revised risk assessment.

Comment:

"An alternative approach to the route-to-route extrapolation would be to estimate an inhalation ADI from the oral ADI, and then combine the hazard quotients and cancer risk."

Response:

While this alternative approach is valid, the staff did not apply it because it is not clear how this approach would reduce the uncertainty.

Comment:

"The CPSC assessment included a nice sensitivity analysis in the exposure assessment, as well as a nice discussion of the exposure uncertainties in the discussion. In contrast, the consideration of toxicological uncertainties for TDCP in the discussion addresses only the sufficiency of data to calculate the ADI and cancer slope factor. A more complete consideration of toxicological uncertainty (qualitative, and, to the degree possible, quantitative), would be useful. This discussion could include uncertainties in the cancer calculation and in the route-to-route extrapolation from oral to inhalation data, as described above. In addition, consideration of the uncertainties addressed by the uncertainty factors and the implications of the overall uncertainty factor would be informative."

Response:

The staff agrees that these are significant sources of uncertainty that merit further discussion, but many are also difficult to quantify. For example, it is not possible to estimate the probability that a given dose response model is correct. However, the discussion section of the revised risk assessment has been expanded to include a more thorough discussion of these sources of uncertainty.

Comment:

"Finally, overall confidence in the derived ADI value can be presented. Such discussion would facilitate readers' understanding of the overall confidence in the estimated ADI and calculated cancer risk. In addition, deeper consideration of uncertainties is consistent with the OMB proposed Risk Assessment Bulletin, although the approaches suggested here are less detailed than many of the approaches recommended in the OMB proposed Bulletin."

Response:

In deriving ADI values, the CPSC staff reviews all of the available data and considers whether the studies were well designed and well executed, as described in the CPSC chronic hazard guidelines (CPSC 1992). Studies are classified as providing inadequate, limited, or sufficient evidence of toxicity. The CPSC staff also discusses sources of uncertainty, such as the completeness of the database.

<u>Triphenyl Phosphate (TPP)</u>

Comment:

"Based on EPA's review of TPP (EPA 2005), the available data on delayed neurotoxicity, adult neurotoxicity, developmental toxicity, and immunotoxicity were judged as negative responses. However, this information is not presented in the current summary document, and much was not presented in the more detailed evaluation by Ferrante (1999a), even though the studies were published prior to that evaluation. While the risk assessment summary document does not necessarily need to include a critical evaluation of all of these studies, it *is* critical that the

summary document present a clear overview of the entire database, so that the endpoints of interest and data gaps are clear."

Response:

The hazard identification section has been expanded, and includes all the available data.

Comment:

"It is indicated in the summary document that the lowest NOAEL reported for TPP was 160 mg/kg-d for effects on body weight gain in male SD rats fed TPP for 90 days in a neurotoxicity screening study (Sobotka et al., 1986). In their publication, Sobotka et al. (1986) stated that their study was a part of a larger subchronic feeding study designed to assess the general toxicity, teratologic effects and immunotoxicity of TPP. In addition, the published part of immunotoxicity report by Hinton et al. (1987) also suggested that the only effects noted were a decreased rate of growth rate and increases in the levels of alpha- and beta-globulins suggestive of increased hepatic activity. All these reports indicated that there might be sufficient dose-response information from the original large subchronic study, and decreased body weight gain is a potential critical effect. Since a well-conducted subchronic study can constitute a minimum database for deriving a safe dose, and decreased body weight is routinely considered as a benchmark in evaluation of whether administrated doses used in a long term experiment reach a maximum tolerable dose, it is recommended that CPSC review the original subchronic study for general toxicity. If possible, CPSC could also contact the authors of that study for relevant unpublished data. The final conclusion and dose response assessment should be based on this additional review and consideration of any additional data."

Response:

The CPSC staff contacted one of the authors of the FDA studies. Unfortunately, the "larger study" was never completed and there are no additional data.

Comment:

<u>Isopropylated Triaryl Phosphate (ITP)</u>

"The CPSC approach to the toxicity evaluation of ITP, and conclusions of that evaluation appear to be reasonable."

<u>Brominated Aryl Esters (BAE's)</u>

"The CPSC approach to the toxicity evaluation of BAE's, and conclusions of that evaluation appear to be reasonable."

Response:

No response required.

Risk Calculations and Other Considerations

Comment:

"Since there was insufficient information to derive ADI values for TPP and ITP, ADI values for other aromatic phosphates, including mixtures, were used as surrogates for TPP and ITP. While the structural analogy among these chemicals suggests that the other aromatic phosphates were appropriate surrogates, it would be useful to present any additional supporting evidence. In particular, a comparison of the available (albeit limited) toxicity data for TPP and ITP compared to other aromatic phosphates would be useful. The Ferrante (1999a) document does a nice job of presenting the data, but it would be useful to present tables directly comparing the toxicity results for the different aromatic phosphates, to aid in the extrapolation. For example, a quantitative comparison between effective doses, (e.g., ED10 or NOAEL), for causing the same toxic effect, (e.g., decrease in body weight), by TPP and other aromatic phosphates in repeated dosing studies would provide strong support for using other data as the surrogate for TPP and other similar compounds in risk assessment."

Response:

The staff expanded the hazard identification to include a brief review of all of the aromatic phosphates.

Comment:

"While the calculation of the LADD for children is correct, it would be useful to explain the calculation a bit more, noting that the child LADD is the exposure as a child, averaged over a lifetime. Conversely, calculation of the HI for the child is conservative (assuming that the exposure and toxicity benchmarks are appropriate and appropriately consider the potential for child sensitivity), since the ADI assumes lifetime exposure, rather than exposure for 2 years."

Response:

Additional explanation was added to the revised risk assessment.

Minor/Editorial Comments

Comment:

"Page 3, the 3rd line from the bottom: A statistical P value of 0.05 is usually used as the criterion in judging whether a observed response is significantly different from the control. The P value for the hepatocellular carcinoma at high dose is less than 0.03 (less than 0.05) as shown in the Table 1 in the summary document. It is not clear why it is still considered: '... **non-significantly** elevated...' "

Response:

This was a typographical error. The text should have said that the response in females, not males, was non-significantly elevated. The response in the males was indeed statistically significant. The text has been revised.

Comment:

"Page 3, the last line: should '... significantly elevated at the high dose in males and the mid- and high dose in females' be '... significantly elevated at the high dose in males and the mid- and high doses in females?' "

Response:

The change has been made.

Comment:

"P. 11 (line just before equation 10): Schwope et al. (1999) should be Schwope et al. (1989). P. 11 (2nd line just after equation 13): It appears that the units for M_P should be mg, not ug. This both keeps the units consistent for equation 13, and appears to be the units used in the spreadsheets."

Response:

The changes were made.

Comment:

"The EPA cancer guidelines are now final (as of 2005). The correct citation is:

U.S. EPA (Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (Environmental Protection Agency). (2005) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available from: <http://www.epa.gov/iris/backgr-d.htm>."

Response:

The reference has been updated.

Reference Listed by the Reviewers

Nobel Functional Chemicals LLC, 2001. High Production Volume (HPV) Challenge Program. Test plan for FYROL FR-2 (Tris[1,3-dichloro-2-propyl] Phosphate.

References Cited by the CPSC Staff

Babich MA (1998) Risk assessment of low-level chemical exposures from consumer products under the U.S. Consumer Product Safety Commission chronic hazard guidelines. Environmental Health Perspectives, 106, Supplement 1: 387-390.

Babich MA (2006) CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. September 2006. Revised draft.

Babich MA, Thomas TA, Hatlelid K (2006) CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. January 2006. Peer review draft.

Cobb D, Bhooshan B (2005) Migration of flame retardant chemicals in upholstered furniture foam. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. December 10, 2005.

Consumer Product Safety Commission (CPSC) (1992) Labeling requirements for art materials presenting chronic hazards; guidelines for determining chronic toxicity of products subject to the FHSA; supplementary definition of "toxic" under the Federal Hazardous Substances Act; final rules. Federal Register 57:46626-46674.

Hughes MF, Edwards BC, Mitchell CT, Bhooshan B (2001) In vitro dermal absorption of flame retardant chemicals. Food and Chemical Toxicology 39: 1263: 1270.

Kiss C (2002) A Mouthing Observation Study of Children Under 6 Years. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. June 2002.

National Research Council (NRC) (2000) Toxicological Risks of Selected Flame-Retardant Chemicals. Subcommittee on Flame Retardant Chemicals, National Research Council, National Academy of Sciences. National Academy Press, Washington, DC.

Rhomberg LR (1997) A survey of methods for chemical health risk assessment among federal regulatory agencies. Presidential/Congressional Commission on Risk Assessment and Risk Management. Washington, DC.

Smith TP, Kiss CT (1998) Empirical observations of children's mouthing behaviors: Frequencies and durations. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. Submitted for publication.

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Memorandum

Date: December 21, 2006

TO : Dale Ray, Project Manager for Upholstered Furniture, Directorate for Economic Analysis

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Michael A. Babich, Ph.D., Chemist, Division of Health Sciences

SUBJECT : Response to Public Comments on the CPSC Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam*

The CPSC staff completed a draft risk assessment on the use of flame retardant (FR) chemicals in upholstered furniture foam in January 2006 (Babich et al. 2006). The risk assessment was part of the January 2006 Briefing Package on Upholstered Furniture. Supresta LLC, a manufacturer of FR chemicals, submitted technical comments on the risk assessment. No other public comments were received. The staff has made appropriate revisions to the risk assessment (Babich 2006), based on comments from peer reviewers and Supresta LLC. Below are the staff's responses to the public comments submitted by Supresta LLC.†

Many of the comments submitted by Supresta LLC involved the factors used to estimate exposure, such as the surface area exposed and the fabric to skin transfer factor. The CPSC staff made several of the suggested changes, which reduced the estimated dermal exposure somewhat. Supresta also commented on the staff's methods for assessing the dose response of TDCP, and suggested changes that would significantly reduce TDCP's cancer potency. The staff disagreed with these comments and did not make the suggested changes. As a result of the changes made in response to the public and peer review comments, the relative contribution of inhalation to total exposure increased. However, the overall conclusions of the risk assessment did not change.

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* These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

† Comments, including tables, references, and appendices, are reported verbatim.

Comment:

"The draft CPSC report compares the health risks associated with two commercial flame retardant products, tris(1,3-dichloro-2-propyl) phosphate (TDCP) and Firemaster™ 550 (FM-550) which consists of a mixture of triphenyl phosphate (TPP), isopropylated triaryl phosphate (ITP), and a proprietary brominated aryl phosphate ester (BAEs)." *

Response:

The CPSC staff risk assessment considered flame retardant (FR) chemicals present in foam samples that were available to the staff. This work was not performed solely as a comparison of two products.

Comment:

"On page 3 of the draft report, the first paragraph under Hazard Identification states "TDCP is acutely toxic by oral administration." This implies that TDCP's oral LD50 is significantly different from that of ITP, melamine, and other flame retardants. The oral LD50 for almost all of the phosphate ester flame retardants is above 2000 mg/kg, indicating low acute oral toxicity. In a 1999 CPSC review of TDCP, Ferrante listed rat acute oral LD50 values of 2.83 g/kg (Celanese study), 3.6 g/kg (Stauffer study) and 2.36 g/kg (CPSC study) (1). An acute oral LD50 test conducted in 1985 in full GLP compliance provides a TDCP oral LD50 of 2.36 g/kg (2). I thus suggest CPSC change the "acutely toxic" language for TDCP."

Response:

As stated by the commenter, TDCP has an oral LD_{50} less than 5,000 mg/kg. Therefore, it is "toxic," as defined by Federal Hazardous Substances Act (FHSA) regulations. 16 CFR 1500.3 (c)(1).

Comment:

"Also in that paragraph, fatty degeneration was described as the only histological lesion in an acute study. Diagnostic pathology is not usually performed in acute tests. I suggest this statement be removed, as the study described by Ferrante is not an acute toxicity test, but rather a repeated dose toxicity test, a copy of which is unattainable for confirmation of the findings."

Response:

The wording has been changed in the revised risk assessment.

* Some of the abbreviations were changed to reflect new information that identifies certain chemicals more specifically. BAE (brominated aryl ester) was changed to OTB (octyl tetrabromobenzoate) and ITP (isopropylated triphenyl phosphate) was changed to PIP (phenol isopropylated phosphate).

Comment:

"On page 3, TDCP is alleged to have reproductive toxicity and is "considered probably toxic to humans" based solely on changes observed in the testes of aging rats in a chronic cancer bioassay. I believe the available data do not support classification as a possible reproductive toxin. In a GLP-compliant fertility study, male rabbits received daily doses of up to 200 mg/kg/day for 12 weeks prior to mating (3, 4)."

Response:

The ADI was based on histopathological effects in the testes, not reproductive function. This is better described as general organ toxicity, rather than reproductive toxicity. This is the same endpoint used by the NRC subcommittee (NRC 2000). The testicular effects were seen in a chronic study in rats, while the reproductive study was of short duration and in a different species. The revised risk assessment explains this point more clearly.

Comment:

"It is known that various changes in the testes of aging rats occur spontaneously and this is confirmed by the 12 month pathology results from the chronic rat bioassay. Rather, TDCP exacerbated the various changes that normally occur in the testes of aging male rats during their second year. Since significant treatment-related changes did not occur in the testes during the first full year of treatment, TDCP should not be considered a reproductive toxin. Rather, I suggest the CPSC utilize the carefully conducted rabbit reproduction study and the pathology report for the 12 month sacrifice in the chronic study as a basis for concluding that TDCP is not a reproductive toxin."

Response:

While these effects did not appear until late in the chronic study, they are still a chronic, degenerative lesion. While these may occur spontaneously, the increased incidence was treatment-related and statistically significant. Therefore, we regarded this as evidence of chronic organ toxicity.

Comment:

"Further, it is clear that the CPSC applied the uncertainty factors published in the NRC 2000 report without due consideration of the science. Since the changes that occurred in the seminal vesicles in the aging male rats do not represent treatment-related testicular toxicity, because they occurred with similar incidence in the control animals, the 5 mg/kg/day dose is, in fact, an NOAEL. Thus, the uncertainty factor of 10 for extrapolating from an LOAEL to an NOAEL should be deleted, as should the factor of 3 for a limited database. This would result in a significantly lower human health risk. The hazard index (HI) would be 0.05 mg/kg-d (uncertainty factors UF_A= 10 for extrapolation from rats to humans; UF_H= 3 intraspecies variability; UF_D= 3 for adequacy of toxicity database)."

Response:

The staff did not apply the same safety factors as the NRC subcommittee. While we regard the NRC report as authoritative and representing the best available science, we evaluated the data and derived the ADI in accordance with the CPSC chronic hazard guidelines (CPSC 1992). This point is discussed in the revised risk assessment. We disagree with the reviewer's conclusion that the increase in incidence was not statistically significant. Our own statistical tests (one-tailed Fisher's exact test) show that these effects are statistically significant (Babich 2006, Table 3).

Comment:

TDCP – Genotoxicity/Carcinogenicity

"In the cancer bioassay, TDCP appears to exacerbate the incidence of benign tumors that normally occur in older rats. There was no significant increase in malignant tumors in any organ in the two-year cancer bioassay. The presence of a non-DNA-reactive, epigenetic mechanism for the induction of the benign tumors is supported by the results of the many genotoxicity tests which, on a weight of evidence basis, confirm that TDCP does not express genotoxicity. While certain Ames Tests showed positive responses, the majority of the microbial mutagenicity tests were negative. TDCP was without genotoxic activity in almost all of the in vitro tests using mammalian cells as test systems. More important, TDCP was consistently without genotoxic activity in the several in vivo mutagenicity tests conducted. Ferrante lists the earlier negative in vivo tests. More recently, a GLP-compliant Mouse Micronucleus Test, conducted twice per OECD Guideline, was negative (5), as was a recently completed in vivo UDS Test, also conducted twice per OECD Guideline, which showed no evidence of UDS (6). While in vitro tests provide a quick, predictive evaluation of mutagenic potential, the more comprehensive in vivo tests provide conclusive indication as to whether a substance has genotoxic activity in the living animal. TDCP was negative in all of the in vivo tests in which it was evaluated. I therefore suggest that the first paragraph on page 4 be revised to reflect the results of the recently conducted mutagenicity tests, and thus indicate that the weight of evidence strongly indicates that TDCP does not have genotoxic activity in the living animal. In that same paragraph, the statement that TDCP is a probable human carcinogen should be deleted, based on a lack of genotoxicity in vivo and a lack of a significant incidence of malignant tumors in any tissue. The exacerbation in the incidence of normally occurring benign tumors late in life should not be interpreted as carcinogenic activity. There is insufficient evidence to conclude that TDCP is a probable human carcinogen. "

Response:

The staff agrees that TDCP is only weakly genotoxic. However, this does not alter our conclusion that TDCP is a probable human carcinogen, as defined in the CPSC chronic hazard guidelines (CPSC 1992). Increased incidence or decreased time to occurrence of spontaneously occurring tumors is generally regarded as evidence of a carcinogenic effect (CPSC 1992).

Comment:

"Under Section 2, Dose Response Assessment, the LOAEL for non-cancer effects should be changed to NOAEL per the previous discussion on changes seen in the control animals at the twelve month interim sacrifice. This would eliminate the uncertainty factor of 10 applied for the extrapolation from an LOAEL to an NOAEL. The RfD would change to 0.05 mg/kg/day."

Response:

The CPSC staff disagrees with this comment. The lack of changes at 12 months is not relevant to the LOAEL or NOAEL in a chronic study.

Comment:

"Examining further the risk calculations, we find that the CPSC calculated the cancer unit risks for adults and children using the linearized multistage model, which assumes a non-threshold genotoxic mechanism. This is consistent with the NRC 2000 report. However, now that new in vivo genotoxicity tests are available which show a lack of genotoxic activity, the determination of the RfD for non-genotoxic cancer effects should use the same calculations used for systemic toxicity. The cancer risk assessment developed by the CPSC without the benefit of the new genotoxicity tests should be deleted from the CPSC report. Based on the NOAEL of 5 mg/kg for carcinogenicity, the RfD would be 0.05 mg/kg/day."

Response:

The lack of genotoxicty does not change the method for estimating cancer risk. Cancer risk is assumed to be linear at low dose unless there is convincing evidence to the contrary (CPSC 1992), such as an understanding of the mode of action (MOA). "Non-genotoxic" is not an MOA. It only means that the MOA does not involve direct mutations. Furthermore, TDCP is weakly genotoxic. It is not completely lacking in genotoxic effects. Therefore, as discussed in the revised risk assessment, a possible role for genotoxicity in tumorigenesis cannot be ruled out.

Comment:

<u>TDCP – Dermal Exposure</u>

"I believe the CPSC basis for determining dermal exposure is overly conservative and uses unrealistic assumptions that result in highly exaggerated exposure and absorption determinations. For example, when estimating dermal exposure of consumers to TDCP from upholstered foam, the CPSC assumed that the consumer is lying on a sofa and wearing a short-sleeved shirt and short pants. The exposed body surface was calculated by adding the surface areas for the lower leg and arms, then dividing by two. This assumes that half of the uncovered body parts is in contact with the sofa. This is an unrealistic overestimation. For essentially circular structures (arms and legs), a more realistic and reasonable estimate would be 20-25% of the total surface are is in contact with the sofa. Even 25% is an exaggeration in that people do not lie stiff, with

elbows and knees locked to provide the proposed contact area. Utilizing the worst case value of 25% of the surface area would result in a 50% reduction in the estimated dermal absorption."

Response:

The assumptions regarding the manner in which consumers interact with upholstered furniture were developed by staff from the CPSC Division of Human Factors. They are intended to be reasonably protective of public health. We agree that the assumption that 50% of the exposed skin contacts the furniture surface is probably an overestimate, due to the 3-dimensional nature (roughly cylindrical) of the legs and arms. However, it is difficult to characterize the contact surface more precisely, especially for a malleable surface such as upholstered furniture. In addition, the softness of upholstered furniture is variable. We chose 50% as a reasonable upper bound. The best estimate is probably between 25% and 50%. In the revised risk assessment, we assumed 33% as a best estimate.

Comment:

"The CPSC discusses exposure by children separately on page 14, using an estimation method developed by EPA many years ago. The body surface areas for children under the age of 2 years were estimated from the median surface area-to-body weight ratio (age 0-2 years: 0.062 [EPA 1997, Table 6-9]). As is apparent from the table, this ratio is highly dependent on age. For example, for children aged 2.1 years the median ratio is 0.042. It is therefore assumed that for children with the selected body weight of 11 kg, using a ratio of 0.062 leads to overestimation of skin surface. In order to refine the estimated body surface area for the selected body weight, it has been suggested that the more refined formula for surface area in relation to length and weight be used (Gehan and George 1970 [in: EPA 1997, Exposure Factors Handbook, Appendix 6A]) instead. This highly regarded formula, $SA = 0.02350 \times H^{0.42246} \times W^{0.51456}$ (SA in m^2, H in cms, W in kg), provides a more accurate estimation of dermal exposure, and is applicable for adults and for children under the age of 5 years (n=229). The estimated body surface for children of the selected weight category (11 kg, equivalent to an age of approximately 12 months and length of 78 cm) is 0.5 m^2. Using this more accurate formula would lead to a reduction of the estimated dermal exposure of children by about 25%."

Response:

The staff generally selected the methods and data recommended in the EPA Exposure Factors Handbook (EPA 1997). However, we agree that the approach suggested by the commenter has merit. Therefore, we adopted the approach suggested by the commenter with minor changes. We substituted parameters that were specific for the age range of interest (0-2 years). We also used the most recent available body weight and length data for infants from the CDC (CDC 2000). Thus, we assumed an average body weight of 10 kg (rather than 11 kg) and a length of 75 cm (rather than 78 cm). Using this method, the total surface area of 1-year-olds was estimated to be 0.48 m^2.

Comment:

"In the CPSC surface migration experiments, Cobb and Bhooshan used miniature furniture mock-ups, 9" x 9" consisting of plywood and foam with a cotton overlay. They applied 25 mL of saline solution directly to the mockup to simulate 8 hours of sweat. The CPSC states that using this wet mock-up and 8 hours of sweat will lead to an overestimation of exposure (page 15), because they really believe daily contact time to be 4 hours. While this, alone, is problematic, there are additional deficiencies in the experimental design. The surface area of the circular filter paper in contact with the mockup measured 23.76 cm^2 (diameter 5.5 cm). This means the moistened mockup (surface area: 523 cm^2) is only partially covered, in contrast to the situation that the test aims to mimic, a person lying on a sofa. Further, there appears to be a calculation error in the draft report. The results from the surface migration experiments (Table 2 in Cobb and Bhooshan 2005) are expressed as μg of flame retardant chemical. Apparently the 8-day average from foams S and Y (3.63 μg) was transferred to the CPSC risk assessment report as mg/cm2 (Table 3). I believe the 0.0036 mg extracted should be converted to mg/cm^2. This results in a migration to liquid phase (M) value of 0.00015 mg/cm^2 instead of the 0.0036 shown in Table 3 for TDCP. This would result in a substantially lower ADD and an HI of below 1.0."

Response:

The migration data were the only data available. Both the estimate of the amount of liquid and the contact time are average values with considerable variability.

We agree that the saline solution was not evenly distributed across the surface of the mock-up. Rather, it was applied to a point on the surface of the mock-up and allowed to distribute by capillary action and hydrostatics. We do not agree, however, that this is inconsistent with consumer exposure. A consumer sitting on a sofa is not exposed to the entire surface.

What appears to be a calculation error is actually a typographic error in the table. This has been corrected in the revised risk assessment.

Comment:

"Furthermore, for estimating the transfer from fabric to skin, the CPSC selectively uses the available information from Wester et al. 1996 and ignores the data for a second substance, glyphosate, for which transfer factors from fabric to skin were determined. Unlike malathion which was dissolved in 50% ethanol, glyphosate was dissolved in water, which more closely resembles sweat. The percutaneous absorption for glyphosate was 1.42%, for immediate exposure to treated fabric 0.74%, declining to 0.08% after one or two days of drying. Remoistening with water resulted in a percutaneous absorption of 0.36%. These figures lead to transfer efficiencies of 0.52 for direct exposure to treated fabric and 0.25 for remoistened fabric. In view of the more relevant solvent, this part of the Wester et al study is more applicable for transfer from upholstered furniture to skin. Even the 0.25 transfer efficiency ratio for glyphosate from the Wester et al study should be considered an exaggeration, as confirmed by a study by Snodgrass (7). He showed that the transfer efficiency of permethrin from impregnated clothing to skin was only 0.005 and was independent of the presence of sweat or the type of

clothing. I therefore believe that a worst case transfer efficiency of 0.25 be used by the CPSC which would result in a 37.5% reduction of the estimated dermal exposure."

Response:

As explained in the draft risk assessment, we selected malathion as a surrogate for FR chemicals because it is more hydrophobic than glyphosate, which is water soluble. The FR chemicals under consideration are hydrophobic.

In considering this comment, we were prompted to search for additional studies on this subject. In addition to the data by Snodgrass, we identified other potential sources of data on the transfer of chemicals from textiles to skin. The data include hydrophobic and water-soluble chemicals and particles. These properties appear to have no effect on surface-to-skin transfer. Considering all of the data, we derived a new estimate of the transfer factor, as well as its upper and lower bounds (Babich 2006, Table 7). This change resulted in a 3-fold lower estimate of surface-to-skin transfer.

Comment:

"The bioavailability of TDCP as a result of dermal absorption is calculated by the CPSC based on the in vitro studies conducted with hairless mouse skin (Hughes 2000; Hughes et al. 2001). The skin of hairless mice is very different from human skin and Hughes et al used acetone as a vehicle for the study. Acetone is known to substantially enhance the transfer of substances through the skin. Thus the use of the Hughes studies for determining bioavailability is inappropriate. Rather, the CPSC should use the results from an industry sponsored in vitro dermal absorption study using human skin and the structurally similar substance TCPP, dissolved in artificial sweat (8, 9). We recognize that the results of this very recent study were not available to the CPSC when the draft report was written. This study was conducted in accordance with the 2004 OECD guidance document for conducting skin absorption studies (10). Accurate measurements were made using ^{14}C-TCPP. The 24-hour absorption after 8 hours contact time was 40 percent, a level that was relatively independent of the concentration. This is equivalent to a dermal absorption rate of 0.05 h^{-1}. The study final report will be made available to the CPSC for consideration of extrapolation to TDCP. This would provide real data using human skin for a substance that has a very similar chemical structure. Using the more accurate dermal absorption rate of 0.05 h^{-1} will result in a 37.5 percent reduction of the internal exposure estimate."

Response:

Dr. Robert Bronaugh, Food and Drug Administration, is a recognized expert in the measurement of percutaneous absorption using *in vitro* methods. Dr. Bronaugh advised us in designing the *in vitro* studies performed by Hughes et al. (2001). The skin from hairless mice was chosen for the *in vitro* percutaneous absorption experiments because it is considered a reasonable surrogate for human skin (Bronaugh et al. 2005). Acetone was used to dissolve TDCP for skin application; then it was allowed to evaporate prior to conducting the experiment. This is a standard method

for the study of extremely hydrophobic compounds. Acetone did not remain on the skin and, therefore, is not likely to affect the permeability of the skin.

The study submitted by the commenter was on the percutaneous absorption of an analog of TDCP, tris(chloropropyl)phosphate (TCPP), using human skin *in vitro*. The commenter cited the results from experiments in which TCPP was present in limiting concentrations. Thus, the absorption rate declined over time, probably following first-order kinetics, as the TCPP on the skin surface was depleted (Bronaugh et al. 2005). The commenters erroneously concluded that TCPP was absorbed at a lower rate through human skin than TDCP was absorbed through mouse skin. Other experiments in the same report applied a larger total volume of TCPP to the skin. In these experiments, the TCPP was not depleted and the absorption rate remained constant throughout the course of the experiment. In these experiments, TCPP was absorbed at roughly the same rate as TDCP.

Comment:

TDCP – New Input Parameters, New Exposure Values and Risk Assessments

"The attached Appendices 1, 2, and 3 contain the CPSC Tables 2, 3, and 4 with corrected fabric to skin transfer, surface area of exposed skin, migration to liquid phase, measured vapor pressure (11), dermal absorption, and acceptable daily intake (ADI) values which have been used to calculate new, more accurate acceptable daily dose (ADD) values and a new hazard Index (HI). Using the new values in Tables 2 and 3, the HI is determined to be 0.01 for adults and 0.02 for children. Certainly the documentation provided in this letter and the articles referenced in the table footnotes support the accuracy of these new values."

Response:

The staff considered each parameter and made changes in the revised risk assessment as appropriate. We reevaluated the fabric-to-skin transfer factor, total skin surface area of children, fraction of skin surface in contact with furniture, and TDCP vapor pressure. These changes are discussed above in more detail. The net effect of these changes reduced the estimated dermal and oral exposure, but increased inhalation exposure. However, the conclusion that TDCP might present a hazard to consumers is unchanged.

Comment:

Melamine – Some Reasons for Concern

"I believe melamine does meet the FHSA definition of toxic, and thus should be reviewed along with TDCP and FM-550. In a National Toxicology Program chronic cancer bioassay, melamine caused transitional cell carcinomas in the urinary bladders of male rats (12). Although bladder stones were found in most of the male rats that expressed bladder cancer, suggesting a correspondence between the presence of stones and bladder tumors, bladder stones were also observed in female rats and in both male and female mice, which did not express bladder tumors. The NTP concluded that melamine is carcinogenic in male rats. The International Agency for

Research on Cancer confirmed that melamine exposure resulted in bladder and urethral carcinomas in male rats and urinary bladder hyperplasia in male mice (13). They indicate that while the tumors "appear to be produced by a non-DNA-reactive mechanism involving epithelial hyperplasia," there was insufficient genotoxicity data available to reach a firm conclusion."

Response:

The bladder tumors induced by melamine are considered to be induced by a mechanism that is not relevant in humans. Therefore, the CPSC staff considers melamine as a possible carcinogen, due to limited evidence in animal studies. This does not satisfy the FHSA definition of "toxic." The discussion on this point has been expanded in the revised risk assessment.

Comment:

"Teratogenic effects of melamine have been reported in toads, where it caused anomalies in the mouth, gills, gonads, and renal tubules (14). In a non-guideline rodent developmental toxicity study, melamine was injected intraperitoneally on two gestation days, with no gross malformations observed. During combustion, melamine decomposes with evolution of poisonous hydrogen cyanide (15). Will this not pose a potential health risk to humans? With the causation of cancer in a rodent bioassay, no reproductive toxicity tests available, and no in vivo mammalian mutagenicity tests, I believe melamine could be considered "toxic" and included in the CPSC review."

Response:

The developmental effects in toads are of uncertain relevance to humans. Smoke toxicity is beyond the scope of this risk assessment.

Comment:

<u>FM-550 – New Toxicity Data</u>

"The report states that because there has been very little testing of two of the three components, ITP and the BAEs, the CPSC used surrogate data to calculate a hazard index, "assuming that TPP and ITP are no more toxic than the other aromatic phosphates." I believe this is an erroneous assumption for ITP, based on toxicology test results recently made public. In a May 5, 2004 TSCA 8(e) substantial risk notification to the U.S. EPA, the manufacturer of FM-550 reported that their commercial ITP caused significant reproductive toxicity in rats. Decreased fertility was observed at all doses, so an NOAEL was not identified. Further, it is not known whether the effect is in the males, females, or in both sexes. Reversibility of the effect was not shown. Litter size and pup survival were also affected. Since FM-550 consists of 24-51% ITP, there could be a significant human reproductive risk associated with exposure to foam containing this flame retardant. In a June 9, 2004 TSCA 8(e) notification, the manufacturer reported significant adverse effects observed in an ITP developmental toxicity study, further justifying concern that both the human fetus and adult may be at risk. I urge the CPSC to carefully

consider the results of these recently conducted studies and not rely on data from surrogate chemicals."

Response:

The May 5, 2004 notice (8e-HQ-0504-15566) provides minimal details. The actual report is not yet available. The same information was described in a recent EPA report (EPA 2005) that we cited in the draft risk assessment. The June 9, 2004 notice (8e-HQ-0604-15587) is for tricresyl phosphate, not ITP (PIP). These reports provide no new information and no changes in the risk assessment are needed.

Comment:

"Page 6 states that there is insufficient information to derive an ADI for isopropylated triaryl phosphate. I believe the lowest dose from the recently conducted reproductive toxicity study, 25 mg/kg/day, can be used as it caused significant reproductive toxicity in that GLP-compliant study. Now there is sufficient information available for the CPSC to conclude that ITP is possibly toxic to humans. The statement on page 7, that there is insufficient data for ITP to derive ADI values, is also no longer accurate."

Response:

As the commenter states, the study is not currently available. We will review the new data when they become available. However, depending on the study design, a reproductive study alone is not necessarily sufficient to derive an ADI. Generally, a 90-day subchronic study with full pathology is needed to provide minimal information for an ADI.

Comment:

"Page 7, Section C implies that since there is insufficient toxicology information to determine whether the BAEs are toxic, they will be treated as non-toxic until shown to be toxic. How does this afford protection for workers and consumers who may be exposed to the BAEs? Shouldn't the OECD Base Set of tests be required of a substance to which infants, children, and adults may have daily contact?"

Response:

Under the FHSA, data showing a toxic effect, i.e., "causing substantial illness or injury," are needed to conclude that a substance is "toxic." 15 USC 1261 (f)(1)(A). In the absence of data, CPSC cannot promulgate a mandatory regulation. The OECD set of tests are not required under the FHSA or the Toxic Substances Control Act (TSCA), which is administered by EPA.

Comment:

"I believe there are several publications that show brominated flame retardants express significant toxicity. For example, recent studies have shown that the polybrominated diphenyl

ether flame retardants adversely affect the central nervous system. They disrupt behavior and impair learning and memory, especially after neonatal exposure (16, 17). The brominated phosphate esters cause genetic recombination in mammalian cells, which can result in various forms of mutation (18). A recent publication by EPA scientists expresses concern over the use of brominated flame retardants after finding significant levels in human tissues and in the environment (19). Recognizing that several brominated flame retardants have neurotoxic and mutagenic activity, how can the CPSC conclude they do not fit the definition of toxic? If FM-550 is to be considered one of the major flame retardants approved for furniture, a responsible course of action would be to require the manufacturer to provide base set toxicity data on the BAEs, either via a SNUR or a consent agreement."

Response:

Brominated FR chemicals (BFR's) are a broad class of compounds with varying toxicological effects. The chemical structure of the BAE's is not closely related to other BFR's for which data are available. FM-550™ was reviewed by EPA under its new chemicals program (EPA 2005). Thus, it has already gone through the same process that would be imposed by a significant new use rule (SNUR). Under the FHSA, CPSC does not have the authority to require additional toxicity tests. However, CPSC can request studies through the EPA Interagency Testing Committee (ITC) or the National Toxicology Program (NTP). The CPSC staff recently requested additional testing of selected FR chemicals, including triaryl phosphates, by NTP.

Comment:

"The statement on page 20 "assuming that TPP and ITP are no more toxic than other aromatic phosphates..." is no longer valid, due to the significant reproductive toxicity reported for ITP. Since there is no NOAEL in the ITP reproduction study, an additional factor should be included in the calculation of risk. The Discussion section begins by exclaiming that there is no toxicity data on FM-550, and insufficient information for ITP, TPP, and BAEs to calculate an ADI value. Yet the toxicity of the three components may be additive or synergistic. It therefore seems reasonable to include an additional 10-fold or 100-fold safety factor in the calculation of risk, rather than making the dangerous and unsupported assumption that the components of FM-550 are no more toxic than other aromatic phosphates."

Response:

We assumed that TPP and ITP were no more toxic than the other members of the class. This is only an assumption and must be supported by data. We have requested additional testing by NTP. We correctly reported that there are limited data for OTB (BAE).

Comment:

"On page 26, the CPSC points out that the estimated upper bound for TPP/ITP exposures would exceed the ADI value for the most toxic aromatic phosphate, then goes on to exonerate FM-550 by stating that doesn't matter because of the inclusion of "several assumptions that tend to overestimate exposure." Doesn't the exposure scenario used for TDCP also include many

conservative assumptions that overestimate exposure? Why is the lack of toxicity data for FM-550 and its components and an inability to measure TPP and ITP not cause for concern?"

Response:

The lack of data in this risk assessment is a significant limitation of the risk assessment, as discussed in the report. The staff did not intend to imply that FM-550™ should be "exonerated." Rather, we pointed out the limitations of the risk assessment.

Comment:

"I believe that a reexamination of the available genotoxicity data, the reproductive toxicity study conducted in rabbits, the 12 month chronic bioassay pathology results, the more accurate dermal absorption values, and the corrected CPSC calculations will result in a conclusion that furniture containing TDCP-treated foam will not present an appreciable health risk to consumers. For FM-550, the results of the reproductive toxicity test should negate the conclusion at the top of page 27 that states "there is no evidence that upholstered furniture containing foam treated with FM-550 would pose an appreciable health risk to consumers." Having no toxicity data should not make a product safer in a health risk assessment than one with considerable data, even if certain of the data indicate a degree of toxicity associated with the product."

Response:

The CPSC staff evaluated these comments in detail and made appropriate changes to the revised risk assessment, as discussed in detail above.

Briefly, we re-evaluated several exposure parameters including the fabric-to-skin transfer coefficient, the estimated total surface area of children, and the fraction of skin surface in contact with upholstered furniture. These revised parameters are close to the values recommended by the commenter, though not identical. These changes reduced the estimated dermal exposure from TDCP.

We considered the *in vitro* percutaneous absorption study with a related FR chemical, tris(chloropropyl) phosphate (TCPP) submitted by the commenter. We disagree with the commenter's interpretation of this study, as well as the commenter's interpretation of the TDCP study that we used (Hughes et al. 2001). We conclude that both studies were of high quality. The data suggest to us that the time course of absorption of TCPP is approximately the same as that of TDCP. There is no justification for using percutaneous absorption data for a surrogate chemical (TCPP) when data from a well-conducted study with the compound of interest (TDCP) are available. If we were to use the TCPP data, the results would not be affected significantly.

The new genotoxicity data submitted by the commenter provide additional evidence that TDCP is probably not genotoxic in animals. However, as explained above, this is not sufficient to change the dose response model that we used to estimate cancer risk.

We also reconsidered the available information on the vapor pressure of TDCP. We chose to use an empirical value obtained in the CPSC Chemistry Laboratory using TDCP-treated foam. We consider that this is more relevant to the current risk assessment than empirical or calculated values for pure TDCP. This change has the effect of increasing the estimated inhalation exposure. However, we recognize that there is considerable uncertainty in estimating inhalation exposure and recommend obtaining additional data.

We disagree with the conclusion of the commenter that the 12-month interim pathology results should be used to derive the ADI. We consider that the lifetime exposure study is more appropriate for assessing chronic toxicity. However, we clarified that the non-cancer ADI is based on chronic organ toxicity, in which the testes were the most sensitive organ site. We do not conclude that TDCP affects reproductive function.

In addition to the public comments discussed here, we also received comments from independent peer reviewers. As a result of all of the comments, the relative contributions of oral and dermal exposure have been reduced, while the relative contribution of inhalation exposure has increased. The conclusion that TDCP might present a hazard to consumers and, therefore, additional data are needed, has not changed.

The reproductive study with FM-550™ described by the commenter is not yet available to us. Therefore, we cannot consider it in our evaluation of FM-550™. We must thoroughly review the study before we can draw any conclusions and evaluate whether it is appropriate for deriving an ADI.

We agree with the commenter that the lack of toxicity data for FM-550™ is not evidence of its safety. We considered all of the available data on the FR chemicals of interest in assessing their potential risks, as described in the chronic hazard guidelines (CPSC 1992). We concluded that basic toxicity and physico-chemical data are needed to assess the potential risks associated with the use of FM-550™ in upholstered furniture.

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Appendix 1*

Table 2. General Input Parameters

Parameter	Best Estimate	Lower Bound	Upper Bound	Reference
Dermal				
Fabric to skin transfer, F [d]	**0.25**	**0.005**	**0.52**	Wester et al. 1996; Snodgrass 1992; see text
Surface area of exposed skin, S, cm^2 [e]	**1,250**	**500**	**4,500**	EPA 1997; Smith 2000
Children [e,f]	**275**	**150**	**1250**	EPA 1997; Smith 2000

[d] Wester et al. 1996, transfer based on experiments with glyphosate in water
[e] 25% of total surface of relevant body parts is in contact with upholstered furniture
[f] Using body surface of 0.5 m^2 for children weighing 11 kg (aged 12 months; length 78 cm)

* The citations in this table refer to the CPSC risk assessment [Note added by the CPSC staff].

Appendix 2

Table 3. Chemical-Specific Input Parameters

Parameter	Symbol	Units	TDCP	TPP/ITP	BAE
Migration to liquid phase	M	mg/cm^2	**0.00015** [g]	0.0011	0.0011
Vapor pressure	VP	torr	**4.2×10^{-8}** [h]	6.3×10^{-6}	$<1 \times 10^{-6}$
Saturation concentration in air	C_{sat}	mg/m^3	**0.001** [i]	0.11	0.015
Dermal absorption rate	K_T	h^{-1}	**0.05** [j]	0.1	0.01
Acceptable daily intake	ADI	mg/kg-d	**0.05** [k]	0.01 - 1.0	ND
Cancer RfD	RfD	mg/kg-d	**0.05** [l]		

[g] corrected for contact surface area in Cobb and Bhooshan 2005 study
[h] Tremain 2002
[i] Calculated from vapor pressure and molecular mass
[j] Based on *in vitro* dermal absorption study with TCPP and human skin
[k] NOAEL for systemic toxicity is 5 mg/kg-d
[l] Threshold model because of non-genotoxic mechanism of tumor formation (NOAEL is 5 mg/kg-d)

Appendix 3

Table 4. Exposure and Risk

Parameter	TDCP		TPP/ITP		BAE	
	Adults	Children	Adults	Children	Adults	Children
ADD (mg/kg-d)	**2.4×10^{-4}**	**5.0×10^{-4}**	2.7×10^{-3}	5.8×10^{-3}	1.8×10^{-3}	3.2×10^{-3}
Percent of total:						
Dermal	**56**	**29**	53	36	80	65
Oral, indirect	**40**	**56**	9	13	14	23
Oral, direct	**0**	**11**	0	2	0	3
Inhalation, vapor	**3**	**5**	38	50	6	9
Inhalation, particles	**0**	**0**	0	0	0	0
HI [m]	**0.005**	**0.010**	0.003 - 0.3	0.006 - 0.6	ND	ND
LADD (mg/kg-d)	**2.4×10^{-4}**	**1.3×10^{-5}**	2.7×10^{-3}	1.6×10^{-4}	1.8×10^{-3}	8.6×10^{-5}

[m] ADI for systemic effects proposed change from 0.005 to 0.05 mg/kg-d