Nomination of FR Chemicals for NTP Testing
U.S. Consumer Product Safety Commission (CPSC) Staff
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Introduction

Upholstered furniture fires are a leading cause of residential fire deaths involving consumer products. The U.S. Consumer Product Safety Commission (CPSC) is considering the development of a performance standard to reduce the potential for ignition of upholstered furniture by cigarettes and small open flames, such as matches, cigarette lighters, and candles (CPSC 2003). Based on 1995-1999 data, the CPSC staff estimates that annually 460 deaths, 1110 injuries, and $130 million in property damage could be addressed by the draft standard (Levenson 2004). While furniture manufacturers would be free to choose the means of complying with a possible standard, manufacturers have informed us that they are likely to treat some upholstery cover fabrics and other upholstery materials with flame retardant (FR) chemicals.

In addressing the hazards associated with upholstered furniture fires, the CPSC staff is working to develop a draft performance standard without creating additional health hazards to consumers, workers, or the environment. In 1998, the Fire Retardant Chemicals Association (FRCA) (now the American Fire Safety Council, AFSC) identified 16 FR chemicals or chemical classes that its members might market for use in upholstered furniture cover fabrics if a standard is promulgated (FRCA 1998). The CPSC staff reviewed all of the available toxicity data on the 16 chemicals/chemical classes, comprising over 50 individual compounds. The toxicity reviews were later updated to include new information (Bittner 2001; Bittner et al. 2001). The CPSC staff reviews contributed to a National Research Council (NRC) report on 16 FR chemicals, representing each of the 16 classes (NRC 2000).

In 2001, the CPSC staff completed risk assessments of selected FR chemicals, including: antimony trioxide (Sb\textsubscript{2}O\textsubscript{3}) (AT); decabromodiphenyl oxide (DBDPO); hexabromocyclododecane (HBCD); phosphonic acid, (3-\{[hydroxymethyl]amino\}-3-oxopropyl)-, dimethyl ester (PA) (sold under the trade name Pyrovatex\textsuperscript{®}); and tetrakis (hydroxymethyl) phosphonium chloride (THPC) (Proban CC\textsuperscript{®}) polymer (Babich and Thomas 2001). Four of these chemicals—AT, DBDPO, HBCD, and PA—are currently used in the United Kingdom (UK), where a flammability standard for upholstered furniture is in effect. Therefore, they may be used in the U.S. if a flammability standard is adopted. THPC also was included in the staff risk assessment, because it is currently used in apparel, and pre-production upholstery fabric samples were available for testing.

With respect to upholstery FR’s in general, the CPSC staff is cooperating with the U.S. Environmental Protection Agency (EPA) to develop a possible significant new use rule (SNUR) on the use of FR chemicals in upholstered furniture. The CPSC staff is also participating in a workgroup with the EPA Design for the Environment (DfE) Program. The DfE workgroup is reviewing the potential risks associated with substitutes for pentabromodiphenyl ether (penta-
BDE). Penta-BDE was the principal FR chemical for flexible polyurethane foam (PUF) used in upholstered furniture. The sole U.S. producer of penta-BDE voluntarily ceased production in 2004 due to concerns about its accumulation in the environment and in human tissue. The European Union and the state of California have banned the production and/or use of penta-BDE and octabromodiphenyl ether (octa-BDE). The EPA has proposed a SNUR for penta- and octa-BDE.

In addition to upholstered furniture, CPSC is considering flammability standards for mattresses and bedding to address small open flame ignitions (CPSC 2004). The state of California is developing flammability standards for upholstered furniture and mattresses. FR chemicals are already used in a variety of products, including televisions, personal computers, carpet, automobile interiors, and infant sleepwear. Recently, the EPA DfE program organized a second workgroup to review the potential risks associated with FR chemicals and barriers for use in mattresses.

The CPSC staff requests that the National Toxicology Program consider performing toxicity tests on selected FR chemicals, as described below.
Antimony Trioxide (Sb$_2$O$_3$) (AT) (1309-64-4)

Antimony trioxide (AT) is a synergist, that is, it is used in combination with halogenated flame retardants, such as decabromodiphenyl oxide. Worker and consumer exposure may occur from FR-treated automobile interiors, infant sleepwear, and home furnishings (FRCA 1998; WHO 1997). Dermal, inhalation, and oral exposure are possible.

The toxicology of AT has been reviewed by the National Research Council (NRC 2000) and the CPSC staff (Babich et al. 2004; Bittner 2001; Bittner et al. 2001; Hatlelid 1999). No lifetime feeding studies are available (Table 1). Sub-chronic studies showed systemic effects (gastrointestinal, hepatic, and hematological effects) at relatively high doses. Inhalation of dusts leads to cancer and non-cancer lung effects in rats. Lung cancer in rats has been attributed to inhalation of “inert particles.” In humans, non-cancer effects occur, but the risk of lung cancer risk is inconclusive due to limited size and follow-up. Risk assessments performed by NRC and the CPSC staff suggest that inhalation of dusts containing AT may be of concern (Babich & Thomas 2001; NRC 2000).

The CPSC staff requests the following studies for AT:
- Chronic oral study in rat and/or mouse
- Chronic inhalation study in a second species, such as the hamster.
Decabromodiphenyl Oxide (DBDPO) (1163-19-5)

Decabromodiphenyl oxide (DBDPO) is an economically important flame retardant that is used in FR-treated high-impact polystyrene (HIPS), electronic equipment, automobile interiors, infant sleepwear, and home furnishings (Birnbaum & Staskal 2004; FRCA 1998; WHO 1997). DBDPO is applied to upholstery and automobile interior cover fabrics in the form of an acrylic or vinyl back-coating. DBDPO is applied to apparel with a polymeric binder (Mischutin 1975). DBDPO is generally used in combination with antimony trioxide. The toxicology of DBDPO has been reviewed (Babich et al. 2004; BFRIP 2003; Birnbaum & Staskal 2004; Bittner 1999a, 2001; Bittner et al. 2001; Hardy 2002; NRC 2000). Adverse effects in the thyroid and liver were observed in rats and mice fed relatively high DBDPO doses in chronic studies (Table 1).

Recently, it has been reported that DBDPO (Viberg et al. 2003a) and lower brominated congeners (Branchi et al. 2002, 2003; Eriksson et al. 2002; Viberg et al. 2002a; Viberg et al. 2003b) may be developmental neurotoxicants in mice, based on changes in spontaneous behavior tests (locomotion, rearing, and total activity) in mice dosed prenatally. However, there are a number of limitations to these studies, and their relevance to human health is uncertain (BFRIP 2003; Birnbaum and Staskal 2004; Eriksson and Viberg 2004; Vijverberg and van den Berg 2004).

The CPSC staff requests the following studies for DBDPO:

- Developmental neurotoxicity studies in rats using established protocols, such as OPPTS 870.6300 (EPA 1998).
Tris(chloropropyl) Phosphate (TCPP) (Mixture of Isomers) (13674-84-5; 76025-08-6; 76649-15-5; 6145-73-9)

Tris(chloropropyl) phosphate (TCPP) has been proposed as a substitute for pentabromodiphenyl ether (penta-BDE) in flexible polyurethane foam (PUF) used in FR-treated home furnishings. Limited toxicity data are available (Bittner 1999d, 2001; Bittner et al. 2001; Ferrante 1999b; NRC 2000) (Table 1). However, some structurally-related compounds are carcinogenic, including tris(1,3-chloropropyl-2) phosphate (13674-87-8) and tris(2,3-dibromopropyl) phosphate (126-72-7).

It should be noted that there has been some confusion in the literature regarding the structure and identity of TCPP (reviewed in Saltzman & Babich 1999). TCPP has been inaccurately referred to as tris(2-chloro-1-propyl) phosphate (6145-73-9), which is a minor component of the commercial product. Both tris(1-chloro-2-propyl) phosphate (13674-84-5) (structure shown) and tris(2-chloro-1-propyl) phosphate (6145-73-9) have been reported to be high production volume chemicals. However, the commercial product is a mixture of isomers containing 57-to-83% tris(1-chloro-2-propyl) phosphate (13674-84-5) (structure shown), 16-to-35% bis(1-chloro-2-propyl) 2-chloro-1-propyl phosphate (76025-08-6), 1-to-7% bis(2-chloro-1-propyl) 1-chloro-2-propyl phosphate (76649-15-5), and less than 1% tris(2-chloro-1-propyl) phosphate (6145-73-9).

The CPSC staff requests the following studies for TCPP:
- Sub-chronic and chronic oral studies in rat and/or mouse.
Phosphonic acid, (3-[[hydroxymethyl]amino]-3-oxopropyl)-, dimethyl ester (PA) (20120-33-6)

Phosphonic acid, (3-[[hydroxymethyl]amino]-3-oxopropyl)-, dimethyl ester (PA) is a reactive flame retardant used with cellulosic fabrics, including children’s sleepwear and upholstered furniture (FRCA 1998; WHO 1997). PA is typically applied in a solution that contains a durable press resin such as trimethylol melamine, phosphoric acid, and ethyleneurea (D’Ruiz 1998; Sanders 1978). The fabric is then dried, heat-cured, and washed. PA thus becomes covalently bound to cellulosic hydroxyl groups and/or the resin (D’Ruiz 1998; Sanders 1978). Unidentified organophosphorus compounds are released when treated fabrics are extracted with aqueous solutions (Cobb 2000; see also Babich & Thomas 2001). These may include cleavage products of PA and/or PA-melamine adducts. The toxicology of PA has been reviewed by the CPSC staff (Babich et al. 2004; Bittner 1999b, 2001; Bittner et al. 2001) and the NRC (NRC 2000). Toxicity data are limited to a 28-day study with incomplete pathology (Table 1).

The CPSC staff requests the following studies for PA:
- Sub-chronic oral studies in rat and/or mouse
- Chronic oral studies in rat and/or mouse, depending on the outcome of sub-chronic studies
- Percutaneous absorption studies in rat and/or mouse
By-product and Metabolite of Tetrakis(hydroxymethyl) Phosphonium Chloride (THPC) (124-64-1):

Tris(hydroxymethyl) phosphine oxide (THPO) (1067-12-5)

Tetrakis(hydroxymethyl) phosphonium chloride (THPC) is a reactive flame retardant used with cellulosic and cellulosic blend fabrics, including FR-treated infant sleepwear and work clothes (FRCA 1998; WHO 1997). It has been proposed for use in upholstered furniture cover fabrics (FRCA 1998). THPC and several application methods were developed as a flame retardant for cotton at the Department of Agriculture, Southern Regional Research Center, New Orleans, LA. In a common commercial process, THPC is first combined with urea to form a 2:1 THPC: urea compound (pre-condensate) (Albright & Wilson 1998; Sanders 1978) (Figure 1). THPC then reacts further with anhydrous ammonia and hydrogen peroxide to form a cross-linked polymer that is physically bound to the fabric.

Multiple organophosphorus compounds are released when treated fabrics are extracted with aqueous solutions (Cobb 2000; see also Babich & Thomas 2001). These compounds are reported to include tris (hydroxymethyl) phosphine oxide (THPO) and low molecular weight polymers (Baitinger 2000; Frank et al. 1982a,b; Loewengart & Van Duuren 1977; Martin 1998; Vail et al. 1982; WHO 2000). THPO and bis-hydroxymethylphosphinic acid (BHPA) are reported to be metabolites of THPC (WHO 2000).
The parent compound, THPC, was toxic to the liver in sub-chronic studies in rodents (Babich et al. 2004; Bittner 1999c, 2001; Bittner et al. 2001; NRC 2000) (Table 1). Little is known regarding the toxicity of THPO. THPO was not mutagenic in Salmonella (MacGregor et al. 1980) and did not inhibit acetyl cholinesterase in vitro (reviewed in WHO 2000).

The CPSC staff requests the following studies for THPO:
- Sub-chronic oral studies in rat and/or mouse
- Chronic oral studies in rat and/or mouse, depending on the outcome of sub-chronic studies
- Percutaneous absorption studies in rat and/or mouse
Aromatic Phosphates:

t-Butylphenyl diphenyl phosphate (BPDP) (56803-37-3)
2-Ethylhexyl diphenyl phosphate (EHDP) (1241-94-7)
Isodecyl diphenyl phosphate (IDDP) (29761-21-5)
Phenol isopropylated phosphate (PIP) (68937-41-7)
Tricresyl phosphate (TCP) (isomers) (1330-78-5)
Triphenyl phosphate (TPP) (115-86-6)

Aromatic phosphates are flame retardant chemicals used in flexible polyurethane foam (PUF) used in FR-treated home furnishings (FRCA 1998; WHO 1997). They may also be used to treat upholstery cover fabrics in the form of a back-coating (FRCA 1998). Workers may be exposed to aromatic phosphates by inhalation of vapor or dusts.

The CPSC staff requests the following studies for representative aromatic phosphates to be selected by NTP:
- Sub-chronic/chronic studies in rat and/or mouse
- Neurotoxicity and/or developmental neurotoxicity studies
Table 1. Toxicity of Selected Flame Retardant Chemicals\textsuperscript{a, b}

<table>
<thead>
<tr>
<th>Chemical/Class</th>
<th>CAS no.</th>
<th>Availability of Toxicity Data</th>
<th>Chronic Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute</td>
<td>Subchronic</td>
</tr>
<tr>
<td>Antimony trioxide (AT)</td>
<td>1309-64-4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Inhalation</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Decabromodiphenyl oxide (DBDPO)</td>
<td>1163-19-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tris(chloropropyl) phosphate (TCPP) (mixture of 4 isomers)</td>
<td>13674-84-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Phosphonic acid, (3-([hydroxymethyl]amino)-3-oxopropyl)-, dimethyl ester (PA) (Pyrovatex\textsuperscript{g})</td>
<td>20120-33-6</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>Tetrakis(hydroxymethyl) phosphonium salts (THPX) (Proban\textsuperscript{h}):</td>
<td></td>
<td></td>
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<tr>
<td>Chloride salt (THPC)</td>
<td>124-64-1</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Sulfate salt (THPS)</td>
<td>55566-30-8</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Compound with urea (THPC-urea)</td>
<td></td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Polymer (THPOH/NH\textsubscript{3})</td>
<td>27104-30-9</td>
<td>?</td>
<td>-</td>
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<tr>
<td>Aromatic phosphates:</td>
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<td></td>
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<tr>
<td>1-Butylphenyl diphenyl phosphate (BPDP)</td>
<td>56803-37-3</td>
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<td>X</td>
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<tr>
<td>2-Ethylhexyl diphenyl phosphate (EHDP)</td>
<td>1241-94-7</td>
<td>X</td>
<td>X</td>
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<td>Isodecyl diphenyl phosphate (IDDP)</td>
<td>29761-21-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Phenol isopropylated phosphate (PIP)</td>
<td>68937-41-7</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Santicizer 141 (&gt;90% EHDP)</td>
<td></td>
<td>X</td>
<td>-</td>
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<tr>
<td>Santicizer 148 (&gt; 90% IDDP)</td>
<td></td>
<td>X</td>
<td>-</td>
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<tr>
<td>Santicizer 154 (TPP + BPDP)</td>
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<td>-</td>
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<tr>
<td>o-Tricresyl phosphate (o-TCP)</td>
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<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Tricresyl phosphate (TCP) mixed isomers</td>
<td>1330-78-5</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Triphenyl phosphate (TPP)</td>
<td>115-86-6</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Adapted from Bittner et al. 2001.

X indicates availability of data; ?, limited data available; -, no data available.

Chronic toxicity as defined under the Federal Hazardous Substances Act 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. Based on oral studies, except where indicated.

Toxic endpoint(s): C, cancer; D, developmental; N, neurotoxic; R, reproductive; O, other (e.g., liver toxicity).

Doses are in mg/kg-d by the oral route, except where indicated. L indicates LOAEL.
References

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Enclosures

CPSC Staff Toxicity Reviews


**CPSC Staff Risk Assessment**


**National Research Council Report**