

Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program. Additional information about the nomination, review, and selection of substances for study by the NTP is provided from *Nominations to the NTP Testing Program* (<http://ntp.niehs.nih.gov/go/nom>).

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## NTP Concept Document: Flame Retardants

### Background

A series of flame retardants (FR) was nominated for National Toxicology Program (NTP) testing by the Consumer Product Safety Commission (CPSC) in 2005. Due to a CPSC regulatory proceeding to reduce fires caused by ignition by small open flames and cigarettes, the use of these FR in upholstered furniture and bedding is expected to increase, thereby increasing the potential for consumer exposure. Nominated compounds included antimony trioxide (AO), decabromodiphenyl oxide (DBDPO), tris(chloropropyl) phosphate (TCPP), phosphonic acid, (3-{{hydroxymethyl}amino}-3-oxopropyl)-, dimethyl ester (PA), tris(hydroxymethyl) phosphine oxide (THPO), and representative aromatic phosphates, selected from tert-butylphenyl diphenyl phosphate (BPDP), isodecyl diphenyl phosphate (IDDP), phenol isopropylated phosphate (3:1) (PIP), 2-ethylhexyl diphenyl phosphate (EHDP), triphenyl phosphate (TPP), and tricresyl phosphate (TCP). Some of these compounds, including AO, DBDPO, and PA are currently in use in the UK, where a similar FR standard is in place. For many if not all of these chemicals, the toxicity database is not sufficient to assess potential health risks. DBDPO was nominated for developmental neurotoxicity study, which is currently being conducted by industry under the EPA HPV chemical program.

### Research Concept

Testing of the chemicals under this project should proceed in three phases. The rationale and the list of chemicals selected for each phase is outlined below.

#### Phase 1

The first phase of the project would include AO and TCPP. Study design for these chemicals would begin immediately.

#### *Antimony Trioxide*

AO typically acts as a synergist for DBDPO and other FR. AO and DBDPO are mixed with a polymer and added to fabrics as a back coating. This process is more cost effective, which is likely to increase use, and may also decrease exposure, as the AO is non-covalently trapped in the polymer. In addition to the CPSC nomination, AO has been nominated by NIEHS. The two nominations cover chronic (oral), chronic (inhalation), and cardiotoxicity testing. Humans are exposed to AO by inhalation, oral, and dermal routes, through both industrial and consumer exposures. In humans, AO exposure has been associated with pulmonary toxicity and lung tumors. However, these results are not definitive due to lack of exposure data and co-exposures that might confound these findings. Cardiotoxicity in humans following exposure to antimony trioxide or other antimony compounds has been noted in a number of human studies. One human study suggested reproductive toxicity in women. The acceptable daily intake ADI for AO is 3.5 mg/kg/day (oral) or 9 ng/m<sup>3</sup> (inhalation).

Subchronic oral and inhalation studies have been conducted in rats. Results were suggestive of hepatic toxicity in Wistar rats receiving AO in the diet. Exposure to AO by inhalation resulted in ocular and pulmonary toxicity in F344 rats. In addition, AO exposure resulted in lung tumors in two of three studies conducted in three different strains of rats (CR Fischer, Wistar, F344), with exposure durations of one year (5-15 month follow up; particles remained in lung past the end of exposure). Both the subchronic and chronic inhalation studies demonstrated some effects in lymph nodes. There is no evidence of toxicity to reproductive organs with subchronic or chronic exposure, and an inhalation developmental toxicity study in rats was negative. However, there is evidence of reproductive and developmental toxicity from other studies. The results of both *in vitro* and *in vivo* genotoxicity studies are mixed.

Subchronic and chronic studies in both rats and mice, by both oral and inhalation routes, with perinatal dosing, were proposed. Assessment of pulmonary toxicity (bronchioalveolar lavage (BAL)/cytokine measurement, inflammation, pulmonary retention, and cell proliferation), genotoxicity (*in vitro* and *in vivo*), reproductive/developmental toxicity, cardiac toxicity (troponin, histopathology, cardiac physiology), and immunotoxicity were proposed based on previous animal and human data. The concept review group agreed that inhalation should be the route of exposure, and that the lung should be the focus of the studies, with the inclusion of both endpoints listed above and endpoints measuring pulmonary function. The group also agreed that cardiotoxicity, reproductive toxicity, and immunotoxicity endpoints should be included in the research program. ADME/TK studies were proposed primarily in order to make comparisons between the inhalation and oral routes; the group agreed with this proposal, and suggested the possible inclusion of mixtures of AO/DBDPO ± polymer. In addition, the group agreed that further characterization of particles, with an emphasis on nanoscale forms, should be performed.

#### *Tris(chloropropyl) phosphate*

TCPP is produced and utilized commercially as a mixture of four isomers. The major component of TCPP is tris(1-chloro-2-propyl) phosphate (57-83%). Other components are bis(1-chloro-2-propyl) 2-chloro-1-propyl phosphate (16-35%), bis(2-chloro-1-propyl) 1-chloro-2-propyl phosphate (1-7%), and tris(2-chloro-1-propyl) phosphate (<1%). A SIDS dossier is available for TCPP. TCPP has been nominated for subchronic and chronic (oral) testing. Use of TCPP may increase, as it has been proposed as a substitute for penta-BDEs in foams. TCPP is present in various indoor environments through its use as a plasticizer. Compounds similar in structure to TCPP (tris(2-chloroethyl) phosphate, tris(1,3-chloropropyl-2) phosphate and tris(2,3-dibromopropyl) phosphate) are carcinogenic. TCPP is found in the atmosphere in household and industrial environments. Although humans are exposed to TCPP by the oral, inhalation, and dermal routes, the toxicity of TCPP in humans has not been evaluated. No acceptable daily intake (ADI) for TCPP has been reported.

The toxicity database on TCPP is limited. Many of the studies were conducted a number of years ago, and composition of TCPP studied may differ from that used presently. One subchronic study was conducted in rats. In this study, there were increases in liver weight (absolute and relative) and kidney weight (absolute) in male and female rats. Histologic damage was seen in the liver, kidney, thyroid, and bone marrow. No effects on reproductive organs were seen in the subchronic study. A developmental study demonstrated non-statistically significant incidences in cervical ribs/missing 13 ribs. TCPP was largely negative in genotoxicity assays, which were primarily conducted using *in vitro* test systems. TCPP was negative for delayed neurotoxicity in hens, and did not significantly inhibit esterases.

A representative commercial mixture was proposed as the test material, but the use of individual isomers, if obtainable, would be considered for acute toxicity or ADME/TK studies. Due to the paucity of toxicity data in rats, the likelihood of a change in the composition of mixtures since toxicity studies were conducted and the lack of study in mice, acute, subchronic, and chronic oral studies, in both rats and mice, with perinatal dosing were proposed. The concept review group determined that the oral route and perinatal dosing were appropriate, that developmental endpoints should be considered for inclusion in subchronic study, and that if significant toxicity was observed in these studies, then the value of testing individual isomers should be addressed. Measurements of thyroid hormones were proposed. However, it was suggested that TCP would likely not modulate these hormones based on structural considerations. Genotoxicity testing was proposed. Since the metabolism of TCP has not been studied and we hypothesize that both substituents of the phosphate group (1-chloro-2-propyl and 2-chloro-1-propyl groups) will form reactive intermediates, ADME studies were proposed. Evaluation of the literature for toxic effects of 1-chloro-2-propanol and 2-chloro-1-propanol, which would form the same intermediates, was suggested by the concept review group.

### **Phase 2**

The second phase of this project would include studies on representative aromatic phosphates (AP), to be selected from BPDP, IDDP, PIP, EHDP, TPP, and TCP. These chemicals are typically produced as mixtures of isomers, and often commercial products containing these chemicals are mixtures. AP were nominated for subchronic and chronic (oral), neurotoxicity and/or developmental neurotoxicity testing.

TCP has been studied previously by NTP (TR 433), and was toxic, but not carcinogenic. Triorthocresyl phosphate (TOCP) is an established neurotoxicant and reproductive toxicant, but was not found in the mixture studied by NTP (<0.1%). Each of these compounds is listed in under the EPA HPV program. BPDP is an orphan HPV, while the others are sponsored HPVs. It was suggested during the concept review that the EPA considers chronic studies on some of these compounds necessary, and follow up to HPV challenge program may be an appropriate mechanism for EPA to assure that these studies are conducted. If NTP is to test these compounds, studies would focus on neurotoxicity and reproductive and developmental toxicity. The toxicity databases on EHDP, TPP, and TCP (and TOCP) are more extensive than those on BPDP, IDDP, or PIP. The concept review group determined that the NTP take an active role in attempting to shape any additional EPA prompted industry studies of these compounds, and to consider filling in research gaps on some selected compounds. A design team should be appointed solely for this task.

### **Phase 3**

The third and final phase of the project would include PA and tris(hydroxymethyl) phosphine oxide (THPO). Both compounds have been nominated for subchronic (oral) study, with the need for chronic study to be determined following the completion of the subchronic study, and assessment of dermal absorption.

During processing, PA becomes bound to fabric, and/or a cross-linking resin that is also added to fabric. Migration studies demonstrated that unidentified organophosphorous compounds were extracted with aqueous solvents. The toxicity database on PA is limited. A 28 day gavage study revealed only a significant increase in spleen/brain ratio and a significant decrease in relative thyroid weight; histopathology on this study was incomplete. Evidence of immunotoxicity has also been reported for PA.

Tetrakis hydroxymethylphosphonium chloride (THPC) forms a large, insoluble polymer in fabric. THPC has been studied by NTP (TR 296) and was found to be toxic, but not carcinogenic. Unidentified organophosphorous compounds were found to migrate from THPC treated fabric upon extraction, and THPO was suspected to be a component in this mixture. Industry indicates that THPO is less toxic than THPC, and that studies to identify and quantify migrating compounds would occur at the end of 2006. Industry also claims that THPC containing fabrics are well washed, and that THPC will not enter the US market.

The concept review group agreed that for both PA and THPO, more information on extractability, especially the identity of migrating compounds, is needed prior to making any decisions regarding study design, and that CPSC should be contacted about coordinating chemistry and dermal absorption studies. It was also suggested that extracts may be more appropriate for testing than pure compounds.

### **Summary**

In summary, chemicals nominated under the FR nomination will be studied in three phases. Study design for AO and TCPP (phase I) would begin immediately. NTP will attempt to partner with EPA and industry to coordinate and compliment testing of aromatic phosphates (phase II). For PA and THPO (phase III), more detailed information on extractability is needed prior to initiating study design on these compounds, and CPSC will potentially be involved in coordinating chemistry and dermal absorption studies. Each compound included in this nomination would be submitted to the HTS faculty for consideration of inclusion in the high throughput program.

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