

Non-halogenated Aromatic Phosphates

Materials for: March 16, 2012 Meeting of Scientific Guidance Panel (SGP)
Biomonitoring California¹

Agenda Item: "Potential Designated Chemicals"

Introduction

At the March 16, 2011 meeting of the Scientific Guidance Panel (SGP), the Panel requested that the Biomonitoring California program prepare a document on "non-halogenated aromatic phosphates" for consideration as potential designated chemicals. Aromatic phosphates all have the common structural element of a phosphate group with at least one ester linkage to an aromatic group. This document provides information relevant to the possible identification of aromatic phosphates as designated chemicals. The information focuses on the criteria for designating chemicals, as specified in Health and Safety Code section 105449:

- Potential for exposure
- Known or suspected health effects
- Need to assess efficacy of public health action
- Availability of a biomonitoring analytical method
- Availability of adequate biospecimen samples
- Incremental analytical cost.

Aromatic phosphates have been used as plasticizers and flame retardants for decades. Some replaced polychlorinated biphenyls (PCBs) for a number of applications. Many are currently marketed as substitutes for polybrominated diphenyl ether (PBDE) flame retardants, which were banned or are being phased out in California.

When aromatic phosphates are added to products as plasticizers or flame retardant, they are not chemically bound. Over time they can migrate out of the products and into the environment. For example, triphenyl phosphate has been found in dust and indoor air. Ethylhexyl diphenyl phosphate is used as a plasticizer in food contact materials and has been found in margarine and candy caramels.

¹ California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

Analytical methods

Analytical methods (LC/ MS-MS) for measuring diphenyl phosphate in urine are available. Diphenyl phosphate is a metabolite of many aromatic phosphates. There is an analytical method (GC/SIM HRMS) for measuring ethylhexyl diphenyl phosphate in breast milk. Some aromatic phosphates have also been measured in consumer products using GC/ MS methods.

Methods would need to be adapted or developed by Program laboratories to analyze for non-halogenated aromatic phosphates, most likely in urine. However, additional research is needed on the most appropriate biological matrix for these compounds. Reference standards are only available for a few of the aromatic phosphates. With regard to incremental analytical cost, it appears that aromatic phosphates can be analyzed as a group. The analysis might also be bundled with other organophosphates.

Need to assess efficacy of public health action

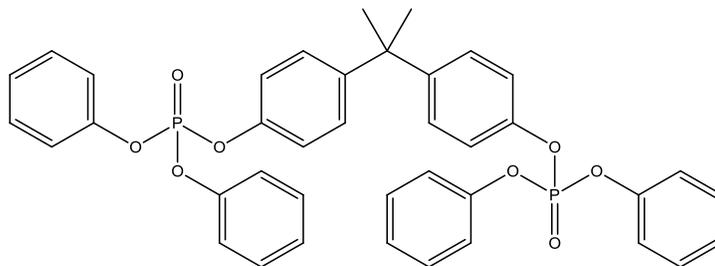
Biomonitoring non-halogenated aromatic phosphates will help the Program determine whether these chemicals are found in California residents and at what level. Biomonitoring will also allow the Program to track whether these levels increase as the use of aromatic phosphates continues to rise.

Eight non-halogenated aromatic phosphates are highlighted in this document:

- Bisphenol A bis(diphenyl phosphate)
- t-Butylphenyl diphenyl phosphate
- 2-Ethylhexyl diphenyl phosphate
- Isodecyl diphenyl phosphate
- Isopropylated triphenyl phosphate
- Resorcinol bis(diphenyl phosphate)
- Tricresyl phosphate
- Triphenyl phosphate

Information on potential exposure, known or suspected health effects and factors related to the potential to biomonitor are summarized for each of these.

Bisphenol A bis(diphenyl phosphate) [CASRN 5945-33-5]



Exposure or potential exposure to the public or specific subgroups:

Bisphenol A bis(diphenyl phosphate) (BDP) is regarded as one of the primary non-halogenated replacements for decaBDE as a flame retardant in electronic enclosures such as TV sets. BDP has use in both PC/ABS² and HIPS/PPO³ plastics (Lowell, 2005). A report for the EU cited known applications relevant to consumers as wire and cable, housings for electric and electronic equipment, textiles, furniture (artificial leather) and flooring (European Commission [EC], 2011).

U.S. production/import volume was listed as 10,000-500,000 pounds in 2002 and 1 - <10 million pounds in 2006 (U.S. EPA, 2002; 2006). BDP (CASRN 5945-33-5) constitutes approximately 85% of the mixture CASRN 181028-79-5, resulting from the reaction of phosphoric trichloride with bisphenol A and phenol. U.S. production/import volume for CASRN 181028-79-5 was first reported in 2002, when it was listed as 1 - 10 million pounds. Production/import volume for the mixture was reported as 10 to < 50 million pounds in 2006. Current production/import volume is not known.

Kemmlin et al. (2003) used a test chamber to measure BDP emissions from a computer system (personal computer [PC], mouse, keyboard, printer) purchased in Germany in 2001. BDP levels were highest at about 20-40 days, reaching steady levels of 20 ng/m³ after approximately 100 days.

Known or suspected health effects:

Few studies on BDP were located. Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2000) reported that genotoxicity studies were negative, and that no treatment-related changes were identified in an oral 28-day study in rats. Washington State (2008) dropped BDP from consideration as an alternative to decaBDE due to concern about its breakdown to bisphenol A (BPA). BPA or a BPA-

² polycarbonate/acrylonitrile butadiene styrene

³ high impact polystyrene/polyphenylene oxide

Non-halogenated Aromatic Phosphates

phosphate derivative may also be a metabolite of BDP. BPA may affect development of the brain, behavior, and prostate (NTP-CERHR, 2008).

Potential to biomonitor:

Physical and chemical properties:

Molecular weight: 692.63

Vapor pressure: $< 9 \times 10^{-6}$ mm Hg (as reported in NICNAS, 2000). Tested BDP contained triphenyl phosphate (1-3%) and residual phenol; 1×10^{-5} , 1.5×10^{-4} mm Hg (reported in EC, 2011).

Water solubility: 0.415 mg/L at 20°C, at a pH between 5.5 and 6 (reported in NICNAS, 2000)

Octanol/water partition coefficient ($\log K_{ow}$): 4.5 or 6 (EC, 2011); >6 (NICNAS, 2000)

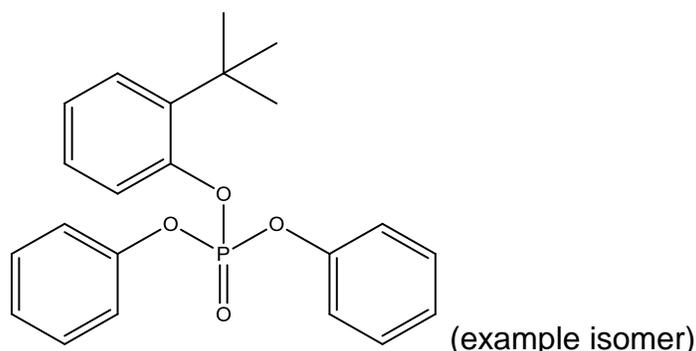
Bioaccumulation (BCF): 3 (estimated, SRC, 2006)

Persistence: Half-lives predicted by PBT Profiler: 60 days, water; 120 days, soil; 540 days, sediment. Review done for Washington State (SRC, 2006) gave BDP a high concern for persistence.

Pharmacokinetics and metabolism: No studies were located.

Past biomonitoring studies: None identified.

t-Butylphenyl diphenyl phosphate (BPDP)
[CASRN 56803-37-3]



Exposure or potential exposure to the public or specific subgroups:

t-Butylphenyl diphenyl phosphate (BPDP, CASRN 56803-37-3) is the major butylated component of the commercial mixture butylated triphenyl phosphate (CASRN 220352-35-2). Non-confidential U.S. production/import volume for the commercial mixture of butylated triphenyl phosphate was reported as 10-50 million pounds in 2006 (U.S. EPA, 2006).

The National Toxicology Program (NTP) identified BPDP as a plasticizer in nail polish and a flame retardant and plasticizer in polyvinyl chloride⁴. The UK Environment Agency (UK EA, 2009a) reported that in 2005, BPDP was primarily used in the EU in PVC; other uses were polyurethane, textile coatings, lubricants and hydraulic fluids. Staff from the U.S. Consumer Product Safety Commission (CPSC) identified BPDP as part of a group of aromatic phosphates that may be used in flexible polyurethane foam (PUF) and that also had potential for use in treated upholstery fabrics (CPSC, 2005).

Stapleton et al. (2011) found several butylated aromatic phosphates in polyurethane foam sampled from children's products, suggesting that these compounds are used in polyurethane foam. Stapleton et al. concluded that the percentages of TPP and butylated aromatic phosphates found in some of the foam were consistent with those of AC073 manufactured by Supresta.

In assessing the commercial mixture butylated triphenyl phosphate (CASRN 220352-35-2), U.S. EPA (2008) concluded that there is a high potential for consumers to be

⁴ NTP Testing Status, available at: <http://ntp.niehs.nih.gov/?objectid=BCEFABB1-123F-7908-7BB4EB183806E7EB>

exposed and that exposures to children might be expected to occur through the household use of some consumer products.

Known or suspected health effects:

In materials submitted to U.S. EPA (2008) for the mixture butylated triphenyl phosphate, reproductive and developmental toxicity were reported at high doses only. The submission to U.S. EPA also reported positive neurotoxicity findings for a study in hens treated with a lubricant containing 3% butylated triphenyl phosphate. Grandjean and Landrigan (2006) included butylated triphenyl phosphate (isomer[s] or mixture not specified) on their list of chemicals that are neurotoxic to humans.

BPDP is among the aromatic phosphates nominated by CPSC staff for NTP testing (CPSC, 2005). BPDP testing may potentially include: *in vitro* studies assessing neurotoxicity, reproductive toxicity, effects on hepatic enzymes and steroidogenesis (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties:

Molecular weight: 382.40

Vapor pressure: 1.4×10^{-6} mm Hg (SRC)

Water solubility: 3.2 mg/L at 25 °C (Saeger et al., 1979). Tested BPDP contained triphenyl phosphate as well as di-t-butylphenyl diphenyl phosphate.

Octanol/water partition coefficient (log K_{ow}): 5.12 (Saeger et al., 1979). As noted above, tested BPDP contained triphenyl phosphate as well as di-t-butylphenyl diphenyl phosphate.

Bioaccumulation (BCF): A range of BCFs were identified. Muir et al. (1983) reported a BCF of 1096 for rainbow trout using one method and 778 using another. Saeger et al. (1979) calculated a BCF of 770.

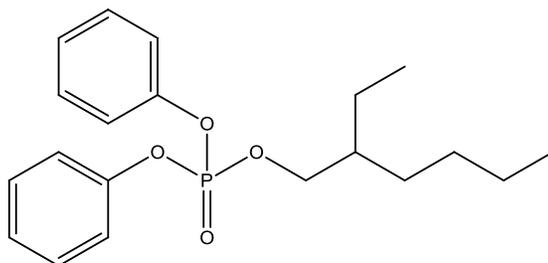
Persistence: Half-lives predicted by PBT Profiler were: 38 days, water; 75 days, soil; 340 days, sediment. UK EA (2009a) chose default half-lives for complete degradation of BPDP as follows: 50 days, surface water; 90 days, soil and sediment.

U.S. EPA (2008) concluded that the butylated triphenyl phosphate mixture [CASRN 220352-35-2], of which BPDP is the main component, has a low potential for persistence.

Pharmacokinetics and metabolism: No information was located.

Past biomonitoring studies: None identified.

2-Ethylhexyl diphenyl phosphate (EHDPP) [CASRN 1241-94-7]



Exposure or potential exposure to the public or specific subgroups:

Ethylhexyl diphenyl phosphate (EHDPP) is primarily a PVC plasticizer (Supresta) with use in food-packaging plastics. NTP reported that EHDPP is used in food-wrapping films and films for tubings for skinless sausages⁵. Uses in the EU reported for 2001 include: PVC, rubber, polyurethanes, photographic films, paints, pigment dispersions, adhesives and textile coatings (UK EA, 2009b). U.S. production/import volume was 1-10 million pounds for 1986 and every year since then (U.S. EPA, 2002; 2006).

In market basket studies from 1991 to 2004, U.S. FDA (2006) found EHDPP most often in candy caramels (24/40 candies tested; mean, 2.47 µg/g; range, 0.05 - 23.5 µg/g) and margarine (22 of 44 samples; mean, 1.2 µg/g; range 0.12 - 7.18). EHDPP was also found in breads at lower levels (e.g., white bread – mean, 0.09427 µg/g; range, 0.010-0.68 µg/g) (U.S. FDA, 2006). In an earlier study (1982-1991), EHDPP was found in 41 of 234 foods tested. It was found most frequently and at highest levels in candy caramels and margarine (U.S. FDA, 1995). Gunderson (1995) calculated mean daily intakes of EHDPP from FDA market basket studies (1986-1991) as 0.339, 1.24, and 0.405 µg/kg body weight/day for ages 6-11 month, 2 years, and 14-16 years, respectively. These calculated intakes were increased from earlier market basket studies (1982-1984) when mean intake for these age groups was calculated as 0.133, 0.602, and 0.208 µg/kg body weight/day (Gunderson, 1988).

EHDPP was found in sewage sludge from various municipal treatment plants (range, 0.32 - 4.6 µg/g) in Sweden (Marklund et al., 2005). EHDPP was found in U.S. reference house dust (Standard Reference Material 2585; n=7) collected in 1993-1994 (1.3 ± 0.12 µg/g) (Bergh et al., 2012). Bergh et al. (2011) also found EHDPP in dust samples from day care centers (median, 0.8 µg/g; range, 0.2-160 µg/g), offices (median, 1 µg/g; range, not detected to 73 µg/g) and private homes (median, 0.5 µg/g;

⁵ NTP Testing Status available at:

<http://ntp-server.niehs.nih.gov/index.cfm?objectid=E87D0766-BDB5-82F8-F1E2FB363AC36412>

range, not detected to 1.8 µg/g) in Sweden. Sundkvist et al. (2010) found EHDPP in bottom-dwelling fish in Sweden at levels of 14,000 ng/g lipid. In studies in Manila Bay, the Philippines, EHDPP was found in 71% of samples (58 fish from 20 different species) at levels up to 740 ng/g lipid (Kim et al., 2011).

Known or suspected health effects:

Summaries of studies submitted to the European Chemical Agency (ECHA) under REACH⁶ include a one-generation reproduction study and a developmental toxicity study in rats. In the reproduction study, increases in adrenal weights were observed in males and females at mid- and high doses. Increased ovary weights and histopathological changes in the ovaries were observed in females at the highest dose tested. Summaries of unpublished 90-day studies describe increased adrenal weights at all doses, vacuolization of the adrenal cortex at mid- and high doses, and hyperplasia of the interstitial gland cells of the ovaries (mid- and high-dose females) in addition to hepatocellular hypertrophy (ECHA, 2012a). Bacterial and mammalian mutagenicity tests *in vitro* and chromosomal aberration tests *in vivo* were reportedly negative (ECHA, 2012a). An older study found no evidence of carcinogenicity of EHDPP fed to rats for two years. This study was not conducted according to current guidelines (ECHA, 2012a).

EHDPP is one of six aromatic phosphates that CPSC staff nominated for NTP testing (CPSC, 2005). EHDPP testing may potentially include: *in vitro* studies assessing neurotoxicity, reproductive toxicity, effects on hepatic enzymes and steroidogenesis (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties:

Molecular weight: 362.41

Vapor pressure): 2.55 x 10⁻⁶ mm Hg at 20°C (estimated, UK EA, 2009b)

Water solubility: 0.051 mg/L (as reported in UK EA, 2009b)

Octanol/water partition coefficient (log K_{ow}): 5.73 (Saeger et al., 1979); 6.64 (reported in Reemtsma et al., 2008).

Bioaccumulation (BCF): 426-934 based on parent compound analysis; 1314 based on radiolabeled [¹⁴C] analysis (as reported in UK EA, 2009b). 1600, calculated (Saeger et al., 1979).

⁶ Registration, Evaluation, Authorization and Restriction of Chemical substances.

Non-halogenated Aromatic Phosphates

Persistence: Half-life in pond water calculated as 3.5 days (Muir et al., 1982). Half-lives predicted by PBT Profiler: 15 days, water; 30 days, soil; and 140 days, sediment. UK EA (2009b) chose default half-lives for complete degradation of EHDPP as follows: surface water, 50 days; soil and sediment, 300 days.

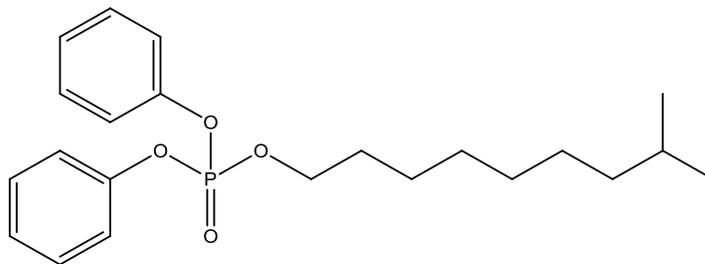
Pharmacokinetics and metabolism:

In rats, approximately 80% of orally administered [¹⁴C]EDHPP was excreted in urine and feces within the first 24 hours. By seven days, nearly half of the administered dose was recovered in urine. Major urinary metabolites were identified as diphenyl phosphate and phenol. EDHPP was widely distributed within two hours of dosing; compared to other tissues, radioactivity was higher in liver and adipose tissue even at seven days, when 99% of radioactivity had been recovered (Nishimaki-Mogami et al., 1988). A study from the 1950s described an experiment in human subjects in which 75-93% of EDHPP was reported eliminated in feces and 5-15% was reported eliminated in urine (ECHA, 2012a).

Past biomonitoring studies:

EHDPP was detected in pooled breast milk samples of Swedish women, at levels ranging from 3.5 - 7.9 ng/g lipid. In the one individual breast milk sample that was analyzed, EHDPP was found at a concentration of 13 ng/g lipid. (Sundkvist et al., 2010).

Isodecyl diphenyl phosphate [CASRN 29761-21-5]



Exposure or potential exposure to the public or specific subgroups:

Isodecyl diphenyl phosphate (IDDP) was identified in a submission to U.S. EPA as a general purpose plasticizer for most commercial resins (Ferro, 2004). NTP identified a known use of IDDP as a “plasticizer for biodegradable tampon ejectors”⁷. The main use reported in the EU was in flexible PVC; other uses included rubber, polyurethanes, textile coatings, paints and pigment dispersions (UK EA, 2009c). In the United States, production/imports has been reported as 1-10 million pounds from 1986-2006 (U.S. EPA, 2002; 2006).

Known or suspected health effects:

UK EA (2009c) found no information for IDDP on reproductive toxicity or cancer. No treatment-related effects were observed in developmental toxicity studies summarized by UK EA (2009c). An unpublished report from 1986 of a 90-day oral study of IDDP in rats submitted under REACH found a decrease in white blood cell counts, increased red blood cell counts, and increased hematocrit (ECHA, 2012b).

IDDP is one of six aromatic phosphates that CPSC staff nominated for NTP testing (CPSC, 2005). IDDP testing may potentially include: *in vitro* studies assessing neurotoxicity, reproductive toxicity, effects on hepatic enzymes and steroidogenesis (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties:

Molecular Weight: 390.46

Vapor pressure: 2.7×10^{-7} mm Hg (UK EA, 2009c)

Water solubility: 0.011 mg/L at room temperature (UK EA, 2009c)

Octanol/water partition coefficient: $\log K_{ow} = 5.44$ [tested substance contained some triphenyl phosphate and di-isodecyl phenyl phosphate] (Saeger, 1979)

⁷ NTP Testing Status available at: <http://ntp.niehs.nih.gov/?objectid=BD7464CF-123F-7908-7B1B7BECA2933797>

Non-halogenated Aromatic Phosphates

Bioaccumulation: BCF 1100 (Saeger et al., 1979)

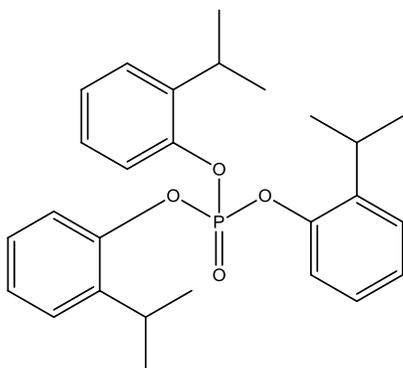
Persistence: Half-life in water, 38 days; soil, 75 days; sediment, 340 days (predicted, PBT Profiler). UK EA (2009c) chose default half-lives for complete degradation of IDDP as follows: surface water, 150 days; soil and sediment, 3000 days.

Pharmacokinetics and metabolism: No information was identified.

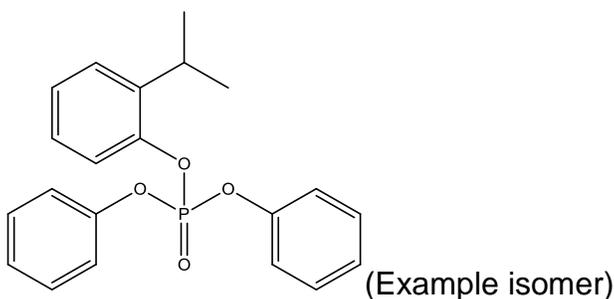
Past biomonitoring studies: None identified.

Isopropylated triphenyl phosphate [CASRN 68937-41-7] (unspecified mixture)

**Tris(isopropyl)phenyl phosphate (TIPP)
[CASRN 26967-76-0] (mixed isomers)**



**Isopropyl phenyl diphenyl phosphate (IPDP)
[CASRN 28108-99-8] (mixed isomers)**



Exposure or potential exposure to the public or specific subgroups:

Isopropylated triphenyl phosphate (IPTPP) is a mixture of as many as 50 unspecified isomers, ranging from isopropyl phenyl diphenyl phosphate (shown above) to tris(isopropylphenyl) phosphate (TIPP, shown above) (U.S. EPA, 2010; UK EA, 2009d). Different commercial products contain various amounts of the different isomers as well as varying amounts of triphenyl phosphate. According to the Nordic Expert Group, commercial formulations can contain from 4-40% triphenyl phosphate (NEG, 2010). Annual U.S. production/import volume of the mixture isopropylated triphenyl phosphate [CASRN 68937-41-7] has been reported at 10-50 million pounds every year since 1986 (U.S. EPA, 2002; 2006). Use in Scandinavian countries was reported to have increased 3-fold from 2004 to 2007 (NEG, 2010).

Producers/importers of IPTPP assert confidentiality for commercial and consumer uses (U.S. EPA, 2010). Some isomers are components of Firemaster 550, a flame retardant mixture for polyurethane foam, although the exact composition of the formulation is a trade secret. The material data safety sheet for Firemaster 550 indicates that the mixture contains 24-51% IPTPP (Chemtura, 2006). IPTPP is also used in a range of PVC products, including coatings on fabrics, adhesives, paints, lubricants and hydraulic fluids (UK EA, 2009d; NEG, 2010).

Sjodin et al. (2001) detected mono-substituted IPTPP (isopropylphenyl diphenyl phosphate) in air samples from an electronics equipment recycling facility in Sweden at levels ranging from 3.4 -100 ng/m³ (depending on the specific recycling activity), indicating their use in electronic equipment.

IPTPP was found in soil samples at two U.S. Air Force bases, one of which had been closed since the 1950s but was used for private aircraft. At one base, a sample contained 5.8 µg/g IPTPP. At the other base, two samples around ground equipment maintenance area contained 0.9 and 2.0 µg/g IPTPP (David and Seiber, 1999).

Known or suspected health effects:

Potential adverse health effects of isopropylated triphenyl phosphate isomers (IPTPP) have not been well studied. In summarizing material on IPTPP submitted for its High Production Volume (HPV) Challenge Program, U.S. EPA (2010) noted that for some endpoints, submitted data were inadequate (repeated-dose toxicity, gene mutations). Based on studies at high doses, U.S. EPA (2010) considered IPTPP to be neurotoxic to hens. A repeated dose toxicity study in rats found effects on ovary, epididymal, adrenal, and liver weights (ECHA 2012c). A two-generation reproduction study, teratology, and 90-day oral studies are planned for 2012 according to the ECHA website.

In *in vitro* studies, IPTPP isomers activated two human nuclear hormone receptors, the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) (Honkakoski et al., 2004). Eight out of nine tested IPTPP isomers activated CAR (2.5-5.5-fold); the ninth inhibited CAR activity. All tested IPTPP isomers activated PXR by approximately 2-4-fold. These receptors regulate the expression of important drug metabolizing enzymes (e.g. cytochrome P450 isozymes). It has been shown that CAR is switched off *in vitro* by two testosterone metabolites (summarized in Li and Wang, 2010). PXR is involved in the expression of the cytochrome P450 isozyme CYP3A4 and certain sulfotransferase isozymes. Activation of PXR might affect androgen levels by induction of CYP3A4 and sulfotransferase isozymes which hydroxylate and conjugate testosterone (Zhang et al. 2010). PXR may also play a role in cholesterol metabolism and lipid homeostasis (Zhou et al., 2009).

Honkakoski et al. (2004) found that specific IPTPP isomers had different effects on human androgen receptor (AR) activity. In the presence of testosterone, di- and tri-substituted *p*-IPTPPs increased AR activity by over 100%; AR activity was decreased 30-40% by di-substituted *o*-IPTPP. Without added testosterone, mono-substituted *p*-IPTPP decreased AR activity by 40-50%. In addition to effects on AR activity, mono-substituted *p*-IPTPP increased estrogen receptor activity by 32%, in the presence of estrogen.

IPTPP was one of six aromatic phosphates nominated to NTP by the U.S. Consumer Product Safety Commission (CPSC) staff (CPSC, 2005) for testing. NTP is considering IPTPP for initial in-depth *in vivo* studies (NTP, 2010b). The testing may include a modified one-generation study in rats with separate cohorts to test for neurotoxicity, immunotoxicity, and reproductive and developmental toxicity. The testing will also include studies in adult mice (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties of tris(isopropyl phenyl) phosphate (TIPP) (tri-substituted IPTPP)

Molecular weight: 452.54

Vapor pressure: 1.725×10^{-8} mm Hg at 20°C (estimated, reported in UK EA, 2009d)

Water solubility: 0.12 mg/L (estimate reported in UK EA, 2009d)

Octanol/water partition coefficient (log K_{ow}): 6.1 (estimated, UK EA, 2009d)

Bioaccumulation (BCF): 1,986 (calculated, UK EA, 2009d)

Persistence: PBT Profiler predicted half-lives: 60 days, water; 120 days, soil; 540 days, sediment. UK EA (2009d) chose default half-lives for complete degradation of TIPP as follows: surface water, 150 days; soil and sediment, 3000 days.

Physical and chemical properties of isopropylphenyl diphenyl phosphate (mono-substituted IPTPP)

Molecular weight: 368.37

Vapor pressure: 7.125×10^{-8} mm Hg at 20°C (estimated, reported in UK EA, 2009d)

Water solubility: 2.2 mg/L at 25°C [measured material also contained TPP and dialkylphenyl phenyl phosphate contaminants] (Saeger, 1979).

Octanol/water partition coefficient (log K_{ow}): 5.31 [measured material also contained TPP] (Saeger, 1979).

Bioaccumulation (BCF): 564 (as reported by UK EA, 2009d); 970 (calculated by Saeger et al., 1979)

Non-halogenated Aromatic Phosphates

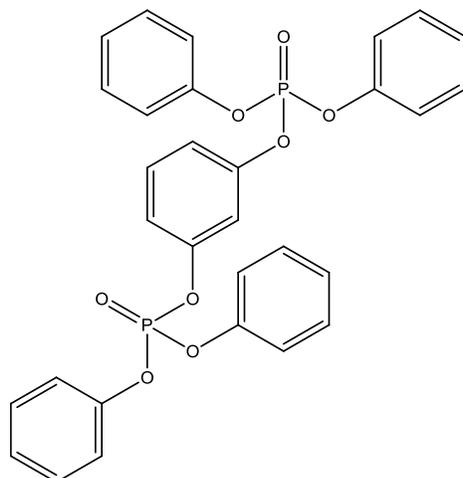
Persistence: UK EA (2009d) chose default half-lives for complete degradation of isopropylphenyl diphenyl phosphate as follows: water, 50 days; soil and sediment, 900 days. PBT Profiler predicted half-lives: 38 days, water; 75 days, soil; 340 days, sediment.

Pharmacokinetics and metabolism:

No information was located.

Past biomonitoring studies: None identified.

Resorcinol bis(diphenyl phosphate) [CASRN 57583-54-7]



Exposure or potential exposure to the public or specific subgroups:

Resorcinol bis(diphenyl phosphate) (RDP) is regarded as a primary substitute for decaBDE in electronic enclosures such as television sets (WA State, 2008). RDP is used in both HIPS/PPO and PC/ABS plastics (Lowell, 2005). In addition to its major use in thermoplastics/styrene polymers, other uses reported in the EU are in PVC plastics, polyurethanes, paints and coatings and pigment dispersions (UK EU, 2009e). A manufacturer's website indicates RDP applications: including appliance housing, business machines, consumer electronics, TV housings, mattresses and insulation (from WA State, 2008).

In 2006, U.S. production/import volume for RDP was reported as up to 500,000 pounds (U.S. EPA, 2006). U.S. production/import volume for CASRN 125997-21-9, the mixture resulting from the reaction of phosphoric trichloride with resorcinol, was reported as 1-10 million pounds U.S. EPA (2006). RDP is the main component of this mixture, constituting 65-80% of it. This mixture also contains from 1-5% of triphenyl phosphate as a contaminant. The bis[3-[(diphenoxyphosphinyl)oxy]phenyl] phenyl ester of phosphoric acid [CAS # 98165-92-5] comprises the remaining 15 to 30% (WA State, 2008).

Kemmlin et al. (2003) measured RDP emissions from a computer system (PC, mouse, keyboard, printer) purchased in 2001 in Germany. RDP levels were highest at about 20-40 days, reaching steady levels of 13 ng/m³ after approximately 100 days.

Known or suspected health effects:

UK EA (2009e) summarized available toxicity studies for RDP, including two 28-day repeated dose toxicity studies, one of which looked at immunotoxicity and neurotoxicity endpoints. A decrease in plasma cholinesterase activity was observed in mice, but this effect disappeared during a 60-day recovery period. The UK EA description of a two-generation reproductive toxicity notes that sexual maturation was significantly delayed in F1 rats, which the study authors attributed to decreased food consumption and bodyweights. Increased adrenal weights and hepatic periportal hypertrophy were attributed to increased stress and induction of cytochrome P-450 isozymes, respectively (UK EA, 2009e). A teratology study in rabbits was negative (Ryan et al., 2000).

Resorcinol is a minor metabolite of RDP. It may have an effect on thyroid hormone function (Thienpont et al., 2011; Welsch, 2008).

Potential to biomonitor:

Physical and chemical properties:

Molecular Weight: 574.47

Vapor pressure: 6.5×10^{-8} mm Hg at 20°C (estimated, UK EA, 2009e)

Water solubility: 0.69 mg/L at room temperature (reported in UK EA, 2009e)

Octanol/water partition coefficient (log K_{ow}): 4.93 (reported by WA State, 2008); 5.5 (estimated, UK EA, 2009e)

Bioaccumulation (BCF): 969 (estimated, UK EA, 2009e)

Persistence: A standard biodegradability study found 37% degradation at 28 days and 66% degradation at 56 days (reported in EA (2009). UK EA (2009e) chose default half-lives for complete biodegradation as follows: surface water, 150 days; soil and sediment, 3000 days. Half-lives predicted by PBT Profiler: 38 days, water; 75 days, soil; 340 days, sediment.

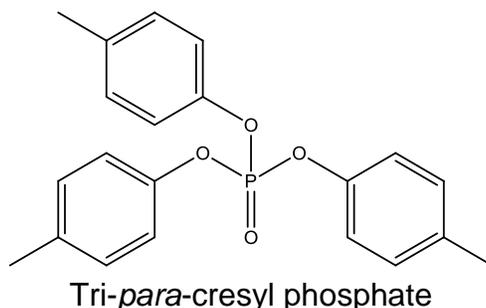
Pharmacokinetics and metabolism:

RDP was extensively metabolized in studies in rats, mice and monkeys and was excreted predominantly in feces in all three species (Freudenthal et al., 2000). Major fecal metabolites were: hydroxy-RDP, dihydroxy-RDP, resorcinol diphenyl phosphate, and hydroxyl-resorcinol diphenyl phosphate. Urinary metabolites were: resorcinol and resorcinol conjugates, resorcinylic glucuronide and resorcinylic sulfate. Rats were treated orally, by inhalation and by dermal administration. Absorption was poor via dermal administration, approximately 20% in rats and 10% in monkeys.

Past biomonitoring studies: None identified

Tricresyl phosphate (TCP) [CAS No. 1330-78-5]

Tri-*ortho*-cresyl phosphate (*o*-TCP) [CAS No. 78-30-8]
Tri-*meta*-cresyl phosphate (*m*-TCP) [CAS No. 563-04-2]
Tri-*para*-cresyl phosphate (*p*-TCP) [CAS No. 78-32-0]



Exposure or potential exposure to the public or specific subgroups:

Tricresyl phosphate (TCP) has been used as a plasticizer for PVC (e.g., automobile and other motor vehicle interiors), as a flame retardant (e.g., backcoating of upholstery fabrics), and as a flame retardant additive for industrial lubricants such as hydraulic and brake fluids (NTP, 1994). The Nordic Expert Group (NEG, 2010) also cites TCP use in paints, lacquers and varnishes in Nordic countries.

U.S. production/import volume was reported as 1-10 million pounds for 1986 and each year since then (U.S. EPA, 2002; 2006). Under current production methods, TCP consists of a mixture of *meta*- and *para*-isomers, with *ortho*-TCP isomers usually at concentrations below 0.1% (NEG, 2010). TCP was recently detected in some Japanese consumer products such as the power board for a LCD-TV (4,500 µg/g), flame retarded curtains (190 µg/g), and wallpaper samples (0.094-0.740 µg/g, n=4) (Kajiwara et al., 2011).

TCP was found in soil samples at U.S. Air Force bases (at levels as high as 130 µg/g) (David and Seiber, 1999), in sediment from Baltimore Harbor (0.4 to 0.6 µg/g) and the Detroit River (0.23 to 1.3 µg/g) (reported by NTP, 1994), and in river and seawater in Japan (67 – 259 ng/L) (Ishikawa et al., 1985). Few studies have looked for TCP in dust. Dust measured in various rooms in a Japanese hotel found levels up to 7.5 µg/g (Takigami et al., 2009). A study in Belgium found TCP in 97% of homes tested (n=33), with levels ranging from < 0.04-5.07 µg/g (mean, 0.44 µg/g) (Van den Eede et al., 2011).

Known or suspected health effects:

o-TCP is neurotoxic, via the formation of a reactive cyclic metabolite. The neurotoxicity of *o*-TCP was discovered in the 1920s when neurological effects including paralysis were traced to consumption of beverages containing Jamaican Ginger that had been adulterated with TCP (NTP, 1994). *o*-TCP is included on a list of chemicals known to be neurotoxic in humans (Grandjean and Landrigan, 2006).

In animal studies summarized by NTP (1994), TCP impaired fertility in both rats and mice and caused testicular and ovarian toxicity. In two-year bioassays, TCP caused cytoplasmic vacuolization of the adrenal cortex (suggesting a possible change in steroid metabolism) (NTP, 1994).

In *in vitro* studies, *p*-TCP activated two nuclear receptors, the human nuclear hormone receptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR) (by > 5-fold and > 2-fold, respectively) (Honkakoski et al., 2004). These receptors regulate the expression of important drug metabolizing enzymes (e.g. cytochrome P450 isozymes). It has been shown that CAR is switched off *in vitro* by two testosterone metabolites (summarized in Li and Wang, 2010). PXR is involved in the expression of cytochrome P450 isozyme CYP3A4 and certain sulfotransferase isozymes. Activation of PXR might affect androgen levels by inducing of CYP3A4 and sulfotransferase isozymes which hydroxylate and conjugate testosterone (Zhang et al. 2010). PXR may also play a role in cholesterol metabolism and lipid homeostasis (Zhou et al., 2009).

TCP is among the aromatic phosphates nominated by CPSC staff for NTP testing (CPSC, 2005). TCP testing may potentially include: *in vitro* studies assessing neurotoxicity, reproductive toxicity, effects on hepatic enzymes and steroidogenesis (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties:

Molecular weight: 368.37

Vapor pressure: 2.6×10^{-7} mm Hg at 20°C (estimated, UK EA, 2009f)

Water solubility (mg/L): 0.36 mg/ml at 25°C (Saeger et al., 1979)

Octanol/water partition coefficient (log K_{ow}): 5.11 (Saeger et al., 1979)

Bioaccumulation (BCF): 165-2768 measured in several fish species (reported in Bolgar et al., 2008); 800, selected by UK EA (2009f) based on a review of available values.

Persistence: Half-lives predicted by PBT Profiler: 38 days, water; 75 days, soil; 340 days, sediment. UK EA (2009f) chose default half-lives for complete degradation of TCP as follows: surface water, 15 days; soil, 30 days; and sediment, 300 days.

Non-halogenated Aromatic Phosphates

Pharmacokinetics and metabolism:

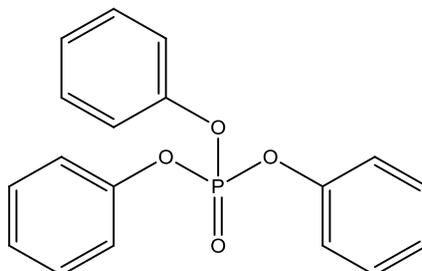
NTP (1994) reported that TCP isomers were well absorbed after oral administration. *o*-TCP was primarily excreted in urine, as was *p*-TCP at low doses; *m*-TCP was primarily excreted in feces at all doses tested.

Kurebayachi et al. (1985) reported that 41% of a single oral dose for *p*-[¹⁴C] TCP was excreted in urine after seven days. At all assessed time periods (24, 73, 168 hours), radioactivity was relatively high in adipose tissue, liver, and kidney. The main urinary metabolites were *p*-hydroxybenzoic acid, di-*p*-cresyl phosphate and *p*-cresyl *p*-carboxyphenyl phosphate.

Past biomonitoring studies:

A marker of *o*-TCP exposure (a butyrylcholinesterase adduct), was found in 6 of 12 blood samples from jet airplane travelers (Liyasova et al., 2011).

Triphenyl phosphate (TPP) [CAS No. 115-86-6]



Exposure or potential exposure to the public or specific subgroups:

Triphenyl phosphate (TPP) is used in PVC and PC/ABS plastics, polyurethane foam, hydraulic fluids, photographic film, lacquers and varnishes, and nail polish (WHO, 1991; Marklund et al., 2003; UK EA, 2009g; U.S. DHHS, 2011). Major areas of use in the EU in 2005 included printed circuit boards, thermoplastic/styrenic polymers, thermosets and epoxy resins, and photographic film (UK EA, 2009g). TPP use in dog flea collars was also reported (UK EA, 2009g). U.S. production/import volume was reported as 10-50 million pounds for the years 1998, 2002, and 2006 (U.S. EPA, 2002; 2006).

In a study of flame retardants in Japanese consumer products, TPP was present at the highest levels of all flame retardants found in the tested products (Kajiwara et al., 2011). The power board for an LCD-TV, for example, had a TPP level of 6,700 µg/g; the front cover of another LCD-TV contained 940 µg/g. TPP levels in the LCD panel for a laptop computer were 2,600 µg/g; the keyboard top contained 500 µg/g. Kajiwara et al. also found TPP in other items (e.g., curtains, 840 µg/g; electrical outlet, 12 µg/g). Other findings include detection in vinyl automobile upholstery (Ahrens et al., 1978).

TPP is also a component of Firemaster 550 and other flame retardant formulations that are added to polyurethane foam (U.S. EPA, 2005). Stapleton et al. (2011) found TPP in foam samples taken from baby products (such as car seats and changing table pads) at levels ranging from 1000 to 9500 µg/g, (mean, 3800 µg/g). Stapleton et al. also reported that TPP was found in every foam sample that contained pentaBDE, suggesting that TPP had been a component of pentaBDE formulations.

Saito et al. (2007) tested the migration of TPP from the outer casings of computer monitors (n=7) and television (TV) sets (n=8). TPP was found in 5 out of 7 computer monitors with median rate of migration of 0.69 µg/m²/h (range: not detected to 20.7 µg/m²/h). TPP was found in 5 out of 8 TV sets with a median migration rate of 0.33 µg/m²/h (range: not detected to 6.7 µg/m²/h). Carlsson et al. (2000) measured TPP emissions from a computer video display unit (VDU) in an experimental "office." This

experiment involved measuring levels in the breathing zone of an imaginary computer operator. On the first day that the computer was switched on, TPP levels of 94 ng/m³ were recorded. TPP levels decreased approximately 40% after the computer had been left on for eight days and were measured as 8.6 ng/m³ after the computer was continuously run for 183 days. Kemmlein et al. (2003) analyzed emissions of TPP from a computer system (PC, mouse, keyboard, printer) in a test chamber and found that TPP levels increased with time. After approximately 100 days, the level of TPP stabilized at 85 ng/m³. Hartmann et al. (2004) reported levels of 1.4-5.7 ng/m³ in electronic store air. In a project that modeled emissions from plastics in Sweden nationwide, TPP was found to be the fifth most emitted plastic additive, with calculated emissions of nearly 4,000 tons/year (Westerdahl et al., 2010).

Marklund et al. (2003) reported high levels of TPP in wipe tests of computer screens and covers (3.3 µg/m² and 4.0 µg/m², respectively). Takigami et al. (2009) detected TPP in dust in a number of rooms in a Japanese hotel at levels ranging from 0.11 – 2.6 µg/g. In Belgium, Van den Eede (2011) found TPP in 100% of house dust samples tested (n=33) with median levels of 0.5 µg/g and a range from 0.04 – 29.8 µg/g. In the U.S., Stapleton et al. (2009) found TPP in 98% of house dust samples tested with a geometric mean value of 7.36 µg/g and range from below the limit of detection to 1,800 µg/g (n=50, homes of men recruited from an infertility clinic). An analysis of a U.S. house dust reference sample (SRM 2585), collected in 1993-1994, found TPP levels of 1.1 ± 0.1 µg/g (n=7) (Bergh et al., 2012).

TPP was detected in reclaimed wastewater at levels ranging from 0.24-1.05 µg/L (mean detected, 0.67 µg/L) (Loraine and Pettigrove, 2006).

TPP was detected in blubber of bottlenose dolphins (n=6) from the Gulf of Mexico [mean 863 ng/g lipid; range 17-3,790 ng/g lipid] (Kuehl and Haebler, 1995). Suckling dolphins had nearly 10 times greater levels than adult males, which the study authors thought may have been related to increased ability of adult animals to metabolize or excrete TPP. TPP was detected in fish from Swedish lakes and coastal areas (e.g., levels in freshwater perch ranged from 21-180 ng/g lipid) (Sundkvist et al., 2010). TPP was found in 45% of fish sampled from Manila Bay, the Philippines; levels ranged from not detected to 350 ng/g lipid (Kim et al., 2011). Kim et al. noted that TPP levels were highest in bottom-dwelling fish.

Known or suspected health effects:

Meeker and Stapleton (2010) reported that TPP levels in house dust were associated with decreased sperm concentration in men (n=50) recruited from an infertility clinic. Altered prolactin levels were also associated with increased levels of TPP in dust. TPP

is included on a list of chemicals known to be neurotoxic in humans (Grandjean and Landrigan, 2006).

In *in vitro* studies, TPP was shown to increase the activities of two human nuclear receptors, the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) by > 5-fold and > 2-fold, respectively (Honkakoski et al., 2004). These receptors regulate the expression of important drug metabolizing enzymes (e.g. cytochrome P450 isozymes). It has been shown that CAR is switched off *in vitro* by two testosterone metabolites (summarized in Li and Wang, 2010). PXR is involved in the expression of cytochrome P450 isozyme CYP3A4 and certain sulfotransferase isozymes. Activation of PXR might affect androgen levels by inducing CYP3A4 and sulfotransferase isozymes which hydroxylate and conjugate testosterone (Zhang et al. 2010). PXR may also play a role in cholesterol metabolism and lipid homeostasis (Zhou et al., 2009).

Honkakoski et al. (2004) reported that TPP decreased human glucocorticoid receptor activity by 20% and decreased human androgen receptor activity by 40-50%. In another study, TPP had moderate binding affinity for the androgen receptor (Fang et al., 2003).

TPP was one of six aromatic phosphates nominated by CPSC staff (CPSC, 2005) for NTP testing. NTP selected TPP as one of two aromatic phosphates for initial in-depth *in vivo* testing. The testing may include a modified one-generation study in rats with separate cohorts to test neurotoxicity, immunotoxicity, and reproductive and developmental toxicity. The testing will also include studies in adult mice (NTP, 2010a).

Potential to biomonitor:

Physical and chemical properties:

Molecular weight: 326.28

Vapor pressure: 9.0×10^{-6} mm Hg at 20°C (estimated, UK EA, 2009g)

Water solubility: 1.9 mg/L (Saeger et al., 1979)

Octanol/water partition coefficient (log K_{ow}): 4.6 (Saeger et al., 1979)

Bioaccumulation (BCF): For rainbow trout, ranged from 271 to 1,368 (UK EA, 2009g); 420 (calculated by Saeger [1979] and selected by UK EA [2009g]).

Persistence: UK EA (2009g) chose default half-lives for complete degradation of TPP as follows: surface water, 15 days; soil and sediment, 300 days. Half-lives predicted by PBT Profiler: 38 days, water; 75 days, soil; 340 days, sediment.

Non-halogenated Aromatic Phosphates

Pharmacokinetics and metabolism:

Sasaki et al. (1984) identified diphenyl phosphate (DPP) as the major TPP metabolite.

Past biomonitoring studies:

Urine:

- Reemtsma et al. (2011) found DPP in the urine of 19 individuals (males and females, ages 14-85 years) in Germany and reported median and 95 percentile of 1.3 µg/L and 28.6 µg/L, respectively.
- Cooper et al. (2011) detected DPP in the urine of nine non-occupationally exposed adults in the United States. DPP levels (normalized to specific gravity) ranged from 0.569 to 63.8 µg/L; the median was 1.8 µg/L.

Blood:

- A method to detect TPP in blood was developed by Shah et al. (2006). TPP detected in plasma samples was attributed to storage in PVC collection bags.

Breast milk:

- Sundkvist et al. (2010) tested breast milk pooled samples and one individual sample of Swedish women, collected two to three weeks after delivery, and found levels of TPP ranging from 3.2 to 11 ng/g lipid (median, 8.5 ng/g lipid).

References:

Ahrens VD, Henion JD, Maylin GA, Leibovitz L et al. (1978). A water-extractable toxic compound in vinyl upholstery fabric. *Bull Environm Contam Toxicol* 20:418-422.

Bergh C, Luongo G, Wise S, Ostman C (2012). Organophosphate and phthalate esters in standard reference material 2585 organic contaminants in house dust. *Anal Bioanal Chem* 402:51-59.

Bergh C, Torgrip R, Emenius G, Ostman C (2011). Organophosphate and phthalate esters in air and settled dust – a multi-location indoor study. *Indoor Air* 21:67-76.

Bolgar B, Hubball J, Groeger J, Meronek S (2008). Handbook for the chemical analysis of plastic and polymer additives. CRC Press. Boca Raton, FL.

Carlsson H, Nilsson U, Ostman C (2000). Video display units: an emission source of the contact allergenic flame retardant triphenyl phosphate in the indoor environment. *Environ Sci Technol* 34:3885–3889.

Chemtura (2006). Material data safety sheet. MSDS Number 00896. Product name: Firemaster 550. Effective date: June 20, 2006. Available at: <http://www.busbrp.org/cireeh/uploads/Main/FM550msds.pdf>. Accessed February 4, 2012.

Cooper EM, Covaci A, van Nuijs ALN, Webster TE, Stapleton HM (2011). Analysis of the flame retardant metabolites bis(1,3-dichloro-2-propyl) phosphate (BDCPP) and diphenyl phosphate (DPP) in urine using liquid chromatography-tandem mass spectrometry. *Anal Bioanal Chem* 401:2123-2132.

David MD, Seiber JN (1999). Analysis of organophosphate hydraulic fluids in US Air Force base soils. *Arch Environ Contam Toxicol* 36:235-241.

Environment Agency (UK EA, 2009a). Environmental risk evaluation report: Tertbutylphenyl diphenyl phosphate (CAS no. 56803-37-3). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQUI-E-E.pdf>

Environment Agency (UK EA, 2009b). Environmental risk evaluation report: 2-Ethylhexyl diphenyl phosphate (CAS No. 1241-94-7). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQTY-E-E.pdf>

Non-halogenated Aromatic Phosphates

Environment Agency (UK EA 2009c). Environmental risk evaluation report: Isodecyl diphenyl phosphate (CAS no. 29761-21-5). Environment Agency. United Kingdom. Available at: <http://publications.environmentagency.gov.uk/PDF/SCHO0809BQUF-E-E.pdf>

Environment Agency (UK EA, 2009d). Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQUG-E-E.pdf>

Environment Agency (UK EA, 2009e). Environmental risk evaluation report: Tetraphenyl resorcinol diphosphate (CAS nos. 57583-54-7). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQUL-E-E.pdf>

Environment Agency (UK EA 2009f). Environmental risk evaluation report: Tricresyl phosphate (CAS no. 1330-78-5). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQUJ-E-E.pdf>

Environment Agency (UK EA 2009g). Environmental risk evaluation report: Triphenyl phosphate (CAS no. 115-86-6). Environment Agency. United Kingdom. Available at: <http://publications.environment-agency.gov.uk/PDF/SCHO0809BQUK-E-E.pdf>

European Chemicals Agency (ECHA). REACH dissemination website (ECHA, 2012a). http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances?p_p_id=48_INSTANCE_Rfk8&_48_INSTANCE_Rfk8_iframe_q=1241-94-7&_48_INSTANCE_Rfk8_iframe_legal=true

European Chemicals Agency (ECHA). REACH dissemination website (ECHA, 2012b). http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7e7a0e-0b74-10c6-e044-00144f67d249/AGGR-3047103b-d03e-44f6-b2b6-ee2bb24319a2_DISS-9c7e7a0e-0b74-10c6-e044-00144f67d249.html#AGGR-3047103b-d03e-44f6-b2b6-ee2bb24319a2

European Chemical Agency (ECHA). REACH dissemination website (ECHA, 2012c). http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7ba203-61e0-4c46-e044-00144f67d249/AGGR-916d6599-61b4-4565-abe0-4f63c65f801b_DISS-9c7ba203-61e0-4c46-e044-00144f67d249.html#AGGR-916d6599-61b4-4565-abe0-4f63c65f801b

European Commission (EC, 2011). Discussion on "Hazardous Substances" Criterion Investigation of Request for Derogation. DRAFT- Work in Progress. Joint Research Center. Institute for Prospective Technological Studies. September 2011. Available at:

<http://susproc.jrc.ec.europa.eu/imaging-equipment/docs/Ecolabel%20Criterion%20Derogations%20Hazardous%20Substances.pdf>

Fang H, Tong W, Branham WS, Moland CL et al. (2003). Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chem Res Toxicol* 16:1338-1358.

Ferro Corporation (Ferro, 2004). High Production Volume (HPV) Challenge Program. Test Plan for Isodecyl Diphenyl Phosphate. December 17, 2004. Available at: <http://www.epa.gov/hpv/pubs/summaries/isodecyl/c14216rt.pdf>

Freudenthal RI, McDonald L, Johnson J et al. (2000). Comparative metabolism and toxicokinetics of ¹⁴C-resorcinol bis-diphenylphosphate (RDP) in the rat, mouse, and monkey. *Int J Toxicol* 19:233-242.

Grandjean P and Landrigan PJ (2006). Developmental neurotoxicity of industrial chemicals. *Lancet* 268:2167-2178.

Gunderson EL (1988). FDA Total Diet Study, April 1982-April 1984, dietary intakes of pesticides, selected elements, and other chemicals. *J AOAC Int* 71:1200-1209.

Gunderson EL (1995). FDA Total Diet Study July 1986-April 1991, dietary intakes of pesticides, selected elements and other chemicals. *J AOAC Int* 78:1353-1363.

Hartmann PC, Burgi D, Giger W (2004). Organophosphate flame retardants and plasticizers in indoor air. *Chemosphere* 57:781-787.

Honkakoski P, Palvimo JJ, Penttila L et al. (2004). Effects of triaryl phosphates on mouse and human nuclear receptors. *Biochem Pharmacol* 67:97-106.

Ishikawa S, Taketomi M, Shinohara R (1985). Determination of trialkyl and triaryl phosphates in environmental samples. *Water Res* 19:119-125.

Kajiwara N, Noma Y, Takigami H (2011). Brominated and organophosphate flame retardants in selected consumer products on the Japanese market in 2008. *J Hazard Mater* 192:1250-1259.

Kemmlin S, Hahn O, Jann O (2003). Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. *Atmos Environ* 37: 5485-5493.

Kim JW, Isobe T, Chang KH, Amano A, Maneja RH, Zamora PB, Siringan FP, Tanabe S (2011). Levels and distribution of organophosphorus flame retardants and plasticizers in fishes from Manila Bay, the Philippines. *Environ Pollut* 159:3653-3659.

Kurebayashi H, Tanaka A, Yamaha T (1985). Metabolism and disposition of the flame retardant plasticizer, tri-p-cresyl phosphate, in the rat. *Toxicol Appl Pharmacol* 77:395-404.

Kuehl DW and Haebler R (1995). Organochlorine, organobromine, metal, and selenium residues in bottlenose dolphins (*Tursiops truncatus*) collected during an unusual mortality event in the Gulf of Mexico, 1990. *Arch Environ Contam Toxicol* 28:494-499.

Li H and Wang H (2010). Activation of xenobiotic receptors: driving to the nucleus. *Expert Opin Drug Metab Toxicol* 6:409-426.

Liyasova M, Li B, Schopfer LM et al. (2011). Exposure to tri-o-cresyl phosphate detected in jet airplane passengers. *Toxicol Appl Pharmacol* 256:337-347.

Loraine GA and Pettigrove ME (2006). Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in southern California. *Environ Sci Technol* 40:687-695.

Lowell Center for Sustainable Production, University of Massachusetts Lowell (Lowell, 2005). Decabromodiphenylether: An Investigation of Non-Halogen Substitutes in Electronic Enclosure and Textile Applications. April 2005. Available at: <http://www.cleanproduction.org/library/Deca%20BDE%20Substitutes%20Report.pdf>

Marklund A, Andersson B, Haglund P (2005). Organophosphorus flame retardants and plasticizers in Swedish sewage treatment plants. *Environ Sci Technol* 39:7423-7429.

Marklund A, Andersson B, Haglund P (2003). Screening of organophosphorus compounds and their distribution in various indoor environments. *Chemosphere* 53: 1137-1146.

Meeker JD and Stapleton HM (2010). House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. *Environ Health Perspect* 118:318-323.

Muir DCG, Grift NP, Lockhart WL (1982). Comparison of laboratory and field results for prediction of the environmental behavior of phosphate esters. *Environ Toxicol Chem* 1:113-119.

Muir DCG, Yarechewski AL, Grift NP (1983). Environmental dynamics of phosphate esters. III. Comparison of the bioconcentration of four triaryl phosphate esters by fish. *Chemosphere* 12:155-166.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2000). Phosphoric acid, (1-methylethylidene) di-4,1-phenylene tetraphenyl ester (Fyrolflex BDP). Full Public Report. File No: NA/773. November 1, 2000. Available at: <http://www.nicnas.gov.au/publications/car/new/na/nafullr/na0700fr/na773fr.pdf>

National Toxicology Program (NTP, 2010a). NTP Research Concept (Update): Selected Flame Retardants. NTP Board of Scientific Counselors Meeting – November 30- December 1, 2010. Draft. Available at: http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/2010/NovDec/12_Selected_flame_retardants_DRC_BSCnov2010.pdf

National Toxicology Program (NTP, 2010b). Concept update: Selected flame retardants (aromatic phosphates). Presentation by M. Behl to the National Toxicology Program Board of Scientific Counselors. December 1, 2010. Available at: http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/2010/NovDec/Presentations/Behl_AromaticPhos.pdf

National Toxicology Program (NTP, 1994). Toxicology and carcinogenesis studies of tricresyl phosphate (CAS No. 1330-78-5) in F344/N Rats and B6C3F₁ Mice (Gavage and Feed Studies). Technical Report 433. U.S. Department of Health and Human Services. National Institute of Health Publication No. 94-3164. Available at: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr433.pdf

National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). CERHR Monograph on the potential for human reproductive and developmental effects of bisphenol A. NIH-Publication No. 5994. September 2008. Available at: <http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf>

Nishimaki-Mogami T, Minegishi K, Tanaka A, Sato M (1988). Isolation and identification of metabolites of 2-ethylhexyl diphenyl phosphate in rats. *Arch Toxicol* 61:259-264.

Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG, 2010). 143. Phosphate triesters with flame retardant properties. Available at: http://gupea.ub.gu.se/bitstream/2077/23825/1/gupea_2077_23825_1.pdf

Non-halogenated Aromatic Phosphates

PBT Profiler. Developed by Environmental Science Center for the Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. Available at: <http://www.pbtprofiler.net/>

Reemtsma T, Lingott J, Roegler S (2011). Determination of 14 monoalkyl phosphates, dialkyl phosphates and dialkyl thiophosphates by LC-MS/MS in human urinary samples. *Sci Total Environ* 409:1990-1993.

Reemtsma T, Quintana JB, Rodil R, Garcia-Lopez M, Rodriguez I (2008). Organophosphorus flame retardants and plasticizers in water and air. I. Occurrence and fate. *Trends Anal Chem* 27:729-737.

Ryan BM, Henrich R, Mallett, E, Freudenthal RI (2000). Developmental toxicity study of orally administered resorcinol bis-diphenylphosphate (RDP) in rabbits. *Int J Toxicol* 19:257-264.

Saeger V, Hicks O, Kaley R et al. (1979). Environmental fate of selected phosphate esters. *Environ Sci Technol* 13:840-844.

Saito I, Onuki A, Seto H (2007). Indoor organophosphate and polybrominated flame retardants in Tokyo. *Indoor Air* 17:28-36.

Sasaki K, Suzuki T, Takeda M, Uchiyama M (1984). Metabolism of phosphoric acid triesters by rat liver homogenate. *Bull Environ Contam Toxicol* 33:281-288.

Shah M, Meija A, Cabovska B, Caruso JA (2006). Determination of phosphoric acid triesters in human plasma using solid-phase microextraction and gas chromatography coupled to inductively coupled plasma mass spectrometry. *J Chromatogr A* 1103:329-336.

Sjodin A, Carlsson H, Thuresson K, Sjodlin S et al. (2001). Flame retardants in indoor air at an electronics recycling plant and at other work environments. *Environ Sci Technol* 35:448-454.

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF (2009). Detection of organophosphate flame retardants in furniture foam and US house dust. *Environ Sci Technol* 43:7490-7495.

Stapleton HM, Klosterhaus S, Keller A et al. (2011). Identification of flame retardants in polyurethane foam collected from baby products. *Environ Sci Technol* 45:5323-5331.

Non-halogenated Aromatic Phosphates

Sundkvist AM, Olofsson U, Haglund P (2010). Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. *J Environ Monit* 12:943-951.

Supresta. Phosflex[®] 362 Product Bulletin. Available at:
<http://supresta.com/pdfs/Phosflex-362-product-bulletin.pdf>

Syracuse Research Corporation (SRC, 2006). Flame Retardant Alternatives (*An assessment of potential health and environmental impacts of RDP and BAPP, two phosphate-based alternatives to Deca-BDE for use in electronics*). Conducted for the Washington State Departments of Health and Ecology. February 2006. Available at: <http://www.ecy.wa.gov/programs/swfa/pbt/docs/flameRetard.pdf>

Syracuse Research Corporation (SRC). PhysProp Database. Available at:
<http://www.syrres.com/what-we-do/databaseforms.aspx?id=386>

Takigami H, Suzuki G, Hirai Y et al. (2009). Flame retardants in indoor air and dust of a hotel in Japan. *Environ Int* 35:688-693.

Thienpont B, Tingaud-Sinqueira A, Prats E, Barata C et al. (2011). Zebrafish eleutheroembryos provide a suitable vertebrate model for screening chemicals that impair thyroid hormone synthesis. *Environ Sci Technol* 45:7525-7532.

U.S. Consumer Product Safety Commission staff (CPSC, 2005). Nomination of FR Chemicals for NTP Testing. August, 1, 2005. Available at:
http://ntp.niehs.nih.gov/files/CPSCFRsnomination_supp_062.pdf

U.S. Department of Health and Human Services (U.S. DHHS, 2011). Household Products Database. Available at: <http://hpd.nlm.nih.gov/cgi-bin/household/list?tbl=TblChemicals&alpha=D>

U.S. Environmental Protection Agency (U.S. EPA, 2005). Furniture Flame Retardancy Partnership. Environmental Profiles of Chemical Flame-Retardant Alternatives for Low-Density Polyurethane Foam. Volume One. EPA 742-R-05-002A. September 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2002). Non-Confidential Inventory Update Reporting Production Volume Information. Toxic Substances Control Act (TSCA) Inventory. Available at: <http://www.epa.gov/oppt/iur/tools/data/2002-vol.htm>

Non-halogenated Aromatic Phosphates

U.S. Environmental Protection Agency (U.S. EPA, 2006). Non-Confidential 2006 Inventory Update Reporting Company/Chemical Records. Toxic Substances Control Act (TSCA) Inventory. Available at: <http://cfpub.epa.gov/iursearch/index.cfm>

U.S. Environmental Protection Agency (U.S. EPA, 2008). Screening-Level Hazard Characterization of High Production Volume Chemicals. Sponsored Chemical. Butylated Triphenyl Phosphate (CAS No. 220352-35-2). [9th CI Name: Phenol, *tert*-Butyl Derivatives, Phosphates (3:1)]. July 2008. Available at: http://www.epa.gov/hpvis/rbp/220352352_Butylated%20Triphenyl%20Phosphate_Web_RBPSuppDocs.July2008.pdf

U.S. Environmental Protection Agency (U.S. EPA, 2010). Screening-Level Hazard Characterization, Sponsored Chemical: Isopropylated Triphenyl Phosphate. Hazard Characterization Document. Available at: http://www.epa.gov/chemrtk/hpvis/hazchar/68937417_Isopropylated%20triphenyl%20phosphate_June%202010.pdf

U.S. Food and Drug Administration (U.S. FDA, 1995). Accumulated pesticide and industrial chemical findings from a ten-year study of ready-to-eat foods. KAN-DO Office and Pesticide Team. *J AOAC Int* 78:614-631.

U.S. Food and Drug Administration (U.S. FDA, 2006). Total Dietary Study. Market Baskets 1991-3 through 2003-4. Available at: <http://www.fda.gov/downloads/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/UCM184304.pdf>

Van den Eede N, Dirtu AC, Neels H, Covaci A (2011). Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust. *Environ Int* 37:454-461.

Washington State Department of Ecology. Washington State Department of Health (WA State, 2008). Alternatives to Deca-BDE in Televisions and Computers and Residential Upholstered Furniture. Final Report. Department of Ecology Publication No. 09-07-041. Department of Health Publication No. 334-181. December 29, 2008. Available at: <http://www.ecy.wa.gov/pubs/0907041.pdf>

Welsch F (2008). Routes and modes of administration of resorcinol and their relationship to potential manifestations of thyroid gland toxicity in animals and man. *Int J Toxicol* 27:59-63.

Non-halogenated Aromatic Phosphates

Westerdahl J, Andersson P, Furhman F, Haglund P et al. (2010). National inventory of emissions of plastic additives from plastic materials. Chemitecs Series Publication Report P4-D4. January 2010. Available at:
http://www.chemitecs.se/download/18.4a08c3cb1291c3aa80e80001152/Chemitecs+P4-D4_final_2010-06-24.pdf

World Health Organization (WHO,1991). *Triphenyl Phosphate*. Environmental Health Criteria 111. Geneva, Switzerland. Available at:
<http://www.inchem.org/documents/ehc/ehc/ehc111.htm#SectionNumber:2.2>

Zhang B, Cheng Q, Ou Z, Lee JH, Xu M et al. (2010). Pregnane X receptor as a therapeutic target to inhibit androgen activity. *Endocrinology* 151:5721-5729.

Zhou C, King N, Chen KY, Breslow JL (2009). Activation of PXR induces hypercholesterolemia in wild-type and accelerates atherosclerosis in apoE deficient mice. *J Lipid Res* 50:2004-2013.