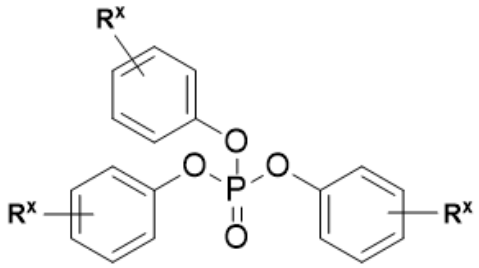
CAS RN 68937-41-7

Substance Name Isopropylated triphenyl phosphate (IPTPP)



Where R^X = H or $CH(CH_3)_2$ and all three rings have at least one -$CH(CH_3)_2$ group.

Uses

In 2016, U.S. manufacturers reported that IPTPP is used as a plasticizer and flame retardant in industrial, commercial, and consumer products, including some children's products[1]. Industrially, it is used as a flame retardant in manufacturing of paint and coatings, adhesives and sealants, transportation equipment, petroleum lubricating oil and grease, hydraulic fluids, and plastic material and resins. It is also used as a plasticizer in paint and coatings manufacturing; an additive in synthetic rubber manufacturing, and a solvent in manufacturing of photographic film paper and photo chemicals [1, 2].

In consumer products, it is used in automotive care products; in photographic supplies, film and photo chemicals; in unspecified plastic and rubber products, and in foam seating and bedding products [1]. IPTPP isomers are a listed ingredient of Firemaster®550 which is used as an additive flame retardant in flexible polyurethane foam [3]. U.S. consumer product testing has identified the profile of flame retardants contained in Firemaster®550 in foam baby products and U.S. upholstered furniture [4, 5].

Manufacturers and U.S. Production Volume

The reported U.S. national production volume (in pounds/year) of IPTPP was 12.4 million in 2010; 15 million in 2011; 3.2 million in 2012; 3 million in 2013; 5.6 million in 2014; and 6 million in 2015. Nine U.S. sites reported importing or manufacturing of this chemical in 2016. One facility, *Univar, Inc.,* is located in Washington State [1, 2].

Toxicity

EPA classified IPTPP a high hazard for reproductive, developmental, and neurological toxicities [6]. Changes in organ weights, reduced fertility and pup survival was observed in an oral rat study of reproduction and development. The lowest observed adverse effect level (LOAEL) was 100 mg/kg-day and the no observed adverse effect level (NOAEL) was 25 mg/kg-day. In a 90-day oral gavage study in rats, a LOAEL of 25 mg/kg-d was identified at the lowest IPTPP dose tested. Observations at 25 mg/kg-day included increased adrenal weights and relative ovary weights and microscopic changes in ovaries in females. Adverse histopathological changes in adrenal glands of both males and females were observed

in all treatment doses. Relative weights of liver, epididymis and adrenal glands were also observed in male rats at higher doses [6, 7]. IPTPP caused neurotoxicity (ataxia and degeneration of the spinal cord and peripheral nerves) in hens at and above a dose of 90 mg/kg-day in a 91-day test [8]. IPTPP inhibited neurotoxic esterase in another hen assay [9]. Brain cholinesterase inhibition was observed in rodent testing of a commercial mixture which contained 80% IPTPP and 20% TPP [6]. There are case reports of neurological symptoms associated with occupational exposure to hydraulic fluids that contained this compound [10]. Inhalation studies with an aerosolized commercial product containing IPTPP were performed for 90 days continuously in rats, hamsters and rabbits. Lethality and pathology were observed at 100 mg/m3 (death in rabbits; pulmonary and heart inflammation, severe degeneration of testicular seminiferous tubules and ovarian hypertrophy in rats). The study reported a no observable adverse effect concentration (NOAEC) of 10 mg/m3. However 25% of female rats in the lower dose group had grossly enlarged adrenal glands, distinct adrenocortical fatty change was observed in all males and females in both exposure groups, and generally with concentration-dependent severity [7].

Very few epidemiological studies have looked for evidence of adverse health effects of IPTPP in people. In a study of Connecticut couples undergoing *in vitro* fertilization (IVF), higher levels of a urinary metabolite of IPTPP (called isopropylphenyl phenyl phosphate or ip-PPP) in women but not men were associated with lower proportion of IVF cycles resulting in successful fertilization, implantation and live births [11, 12]. A North Carolina study reported that IPTPP exposure during pregnancy was associated with timing of delivery [13]. Women in the highest quartile of ip-PPP concentrations in urine delivered female infants 1 week earlier than women with levels in the lowest quartile. There was also increased odds of preterm birth (birth at <37 weeks gestation) for female infants when maternal ip-PPP levels were above vs. below the study's median level. The same trend was not observed for boy infants, in fact, higher maternal ip-PPP was associated with decreased odds of preterm birth in boys. Maternal urine was collected during 2002-2005 [13].

IPTPP was active in a total of ten out of eleven assays used to investigate potential developmental toxicity and neurotoxicity by U.S. Environmental Protection Agency (EPA) and National Toxicology Program scientists [14]. IPTPP was most active in two whole organism assays; inhibiting growth and development of both zebrafish embryos and *C. elegans* larvae (PODs < 5 µM) [14, 15]. To better understand the mechanism of developmental toxicity observed, the authors surveyed Tox21 assays results and reported three areas of relevant biological activity for organophosphate flame retardants: mitochondrial toxicity in mammalian cells, increase of constitutive androstane receptor (CAR) transcriptional factor activity; and decrease of androgen receptor (AR) transcriptional factor activity [15]. Honkakoski et al., 2004 tested a number of different IPTPP isomers specifically for biological activity on both mouse and human receptors *in vitro* [15]. Eight out of nine IPTPP isomers tested activated the human CAR *in vitro*. All nine isomers activated the human pregane X receptor (PXR). Both these receptors are active in regulating enzymes that metabolize and detoxify chemicals but are also involved in steroid hormone metabolism and clearance. Some IPTPP isomers also were active on human androgen receptor (AR) activity. In the presence of testosterone, di-and tri-substituted p-IPTPPs increased AR activity by over 100% [16].

There is emerging evidence that IPTPP may contribute to fat accumulation. In a developmental study of rats, offspring exposed to Firemaster®550 prenatally and through lactation were 30-60% heavier by weaning and were obese as adults [17]. Female offspring also entered puberty sooner and had glucose intolerance. Subsequent *in vitro* investigations have demonstrated that IPTPP ($1-10$ µM) stimulates adipogenesis [18-20] and that at least one pathway of this activity is through activation of peroxisome proliferator-activated receptor gamma (PPARγ) and induction of relevant transcriptional activity [18, 19]. Observations in humans are limited. A case-control study of women residing in Connecticut reported that the urinary level of ip-PPP metabolite was 1.4 times higher in overweight women and 1.7 times higher in obese women compared to women with body-mass index (BMI) <25 [21].

Exposure

IPTPP isomers have not been included in many house dust studies. A recent study of 190 homes in North Carolina, showed widespread detection of individual isopropylated triarylphosphate isomers in indoor dust. One such isomer, called 2IPPDPP, was detected in 81% of dust samples with a mean level of 101.1 ng/g and a 90th percentile of 461 ng/g. In this study, house dust levels of IPTPP correlated with levels measured on hands of young children living in the homes. Hand wipe samples also correlated with urine levels of an IPTPP metabolite in the children [22].

U.S. biomonitoring studies indicate that widespread exposure to adults and children is occurring [11, 13, 21, 23-25]. 80% of urine samples (n=563) from women of reproductive age undergoing IVF treatment in Connecticut were positive for the urinary metabolite ip-PPP. The mean level was 0.23 ng/mL and the 75th percentile level was 0.44 ng/mL [11]. 99% of urine (n=349) from pregnant women in North Carolina were positive for ip-PPP metabolite. The mean level was 6.80 ng/mL, and the 75th percentile was 10.9 ng/mL [13]. Maximum levels detected in women in both these studies were near 70 ng/mL. Both studies collected urine in the mid-2000s. A more recent sample from 2010-2013 showed median values of ip-PPP among 200 women in Connecticut (not pregnant) to be 2.2-2.5 ng/mL and the 75th percentile to be 4.2-4.7 ng/ml. Detection frequency was 100% [21].

In children, aged 3-6 years (*n*=181), participating in a North Carolina Study in 2014 - 2016, all urine samples had measurable ip-PPP. The mean ip-PPP levels in urine was 6.85 ng/ml, the 90th percentile level was 17.6 ng/ml and the maximum was 61.5 ng/ml. The urine sample was a composite of 3 spot urines over 48 hours which is a more stable measurement for metabolites that are rapidly excreted [22]. Ip-PPP metabolite was also measured in urine of children in a 2013-14 study of families in Princeton, New Jersey. Mean and maximum level in the children's urine were 1 ng/mL and 10.1 ng/mL, respectively [24]. Slightly higher mean levels were detected in babies in a 2015 California study population [25].

Environmental Fate and Transport

EPA considered IPTPP to have moderate persistence in the environment and high potential for bioaccumulation [6].

Summary from National Library of Medicine Hazardous Substances Data Bank [10]

If released to air	• IPTPP will exist in both the vapor and particulate phases based on estimated vapor pressure range of constituents. • Vapor-phase IPTPP will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 12 hours. • Particulate-phase IPTPP will be removed from the atmosphere by wet and dry deposition. Long range transport on particles is possible.
If released to soil	• IPTPP will have slight to no mobility in soil based on a range of constituents. • Unlikely to volatilize from moist or dry soil surfaces based upon its negligible solubility in water and low vapor pressure range. • Is not readily biodegradable. Biodegradation data on IPTPP were not available. A similar commercial mixture, Phosflex TXP, was shown to not be readily biodegradable. • Abiotic degradation in soil is also expected to be slow.
If released into water	• IPTPP is expected to adsorb into suspended solids and sediment based upon the K_{oc} range. Volatilization from water surfaces is not expected to be an important fate process based upon its negligible solubility in water and low vapor pressure range. • Photo-degradation pathway is not a significant process. • Hydrolysis is not considered an important environmental fate process given half-lives of greater than 1 year at pH 4 and pH 7.
Bioconcentration and bioaccumulation	• IPTPP has a high potential to bioaccumulate in fish, based on its estimated bioaccumulation factor. • Bioconcentration values of 6.9 to 573 were measured in fish for constituents of IPTPP formulations (triphenyl phosphate and tris (4-isopropylphenyl) phosphate).

Physical-Chemical Properties of IPTPP

IPTPP is not a discrete chemical. It is an isomeric mixture of phosphate esters derived from isopropyl phenols that varies among commercial products. Commercial mixtures may also contain some triphenyl phosphate and isopropylated diphenyl phosphates [6, 9, 26].

Molecular Weight 452 g/mol (typical)

Log K_{ow}	5.44 (measured)
Water Solubility	4.9×10^{-4} mg/L at 25°C (estimated)
Melting Point	< 25° C
Boiling Point	220-270° C at 4 mm Hg (measured)
Vapor Pressure	1.1×10^{-6} – 1.0×10^{-7} mm Hg at 25°C (estimated)
Henry's Law Constant	2.9×10^{-7} atm-m^3/mole (estimated)

Regulatory

EPA considered IPTPP to have very high aquatic toxicity, moderate persistence in the environment and high potential for bioaccumulation [4]. In 2017, EPA listed it as "persistent, bioaccumulative and toxic" under the Toxic Substances Control Act (TSCA) Section 6(h). TSCA requires EPA to skip risk evaluation on PBTs listed under 6(h) and proceed directly to imposing a rule that will reduce their exposure "to the extent practicable". EPA action on this chemical is underway and may pre-empt state policy options.

References

1. EPA, *2016 Chemical Data Reporting (CDR) online database - initial information reported under TSCA*. 2017, US Environmental Protection Agency.
2. EPA, *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Phenol, isopropylated, phosphate (3:1). Support document for Docket EPA-HQ-OPPT-2016-0730.* August 2017, US Environmental Portectins Agency, Office of Chemical Safety and Pollution Prevention
3. Chemtura, *Safety Data Sheet Firemaster 550*. 2015.
4. Stapleton, H.M., et al., *Identification of flame retardants in polyurethane foam collected from baby products.* Environ Sci Technol, 2011. **45**(12): p. 5323-31.
5. Stapleton, H.M., et al., *Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out.* Environ Sci Technol, 2012. **46**(24): p. 13432-9.
6. EPA, *Flame Retardants Used in Flexible Polyurethane Foam: An Alternatives Assessment Update*. 2015, Environmental Protection Agency.
7. ECHA, *Registration Dossier for Phenol, isopropylated, phosphate (3:1); EC number: 273-066-3; CAS number: 68937-41-7*. 2018, European Chemicals Agency (ECHA).
8. Environmental Protection Agency (EPA), *ChemView file for CAS No. 68937-41-7*. 2016.
9. EPA, *Screening-Level Hazard Characterization: Sponsored chemical Isopropylated Triphenyl Phosphate*. 2010.
10. HSDB, *Isopropylated phenol, phosphate; CASRN: 68937-41-7*. 2015, ToxNet Toxicology Data Network, National Library of Medicine.
11. Carignan, C.C., et al., *Urinary Concentrations of Organophosphate Flame Retardant Metabolites and Pregnancy Outcomes among Women Undergoing in Vitro Fertilization.* Environ Health Perspect, 2017. **125**(8): p. 087018.
12. Carignan, C.C., et al., *Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization.* Environ Int, 2018. **111**: p. 232-238.

13. Hoffman, K., et al., *Prenatal exposure to organophosphates and associations with birthweight and gestational length.* Environ Int, 2018. **116**: p. 248-254.
14. Behl, M., et al., *Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity.* Neurotoxicol Teratol, 2015.
15. Behl, M., et al., *Editor's Highlight: Comparative Toxicity of Organophosphate Flame Retardants and Polybrominated Diphenyl Ethers to Caenorhabditis elegans.* Toxicol Sci, 2016. **154**(2): p. 241-252.
16. Honkakoski, P., et al., *Effects of triaryl phosphates on mouse and human nuclear receptors.* Biochem Pharmacol, 2004. **67**(1): p. 97-106.
17. Patisaul, H.B., et al., *Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster(R) 550 in rats: an exploratory assessment.* J Biochem Mol Toxicol, 2013. **27**(2): p. 124-36.
18. Pillai, H.K., et al., *Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro.* Environ Health Perspect, 2014. **122**(11): p. 1225-32.
19. Tung, E.W.Y., et al., *Firemaster(R) 550 and its components isopropylated triphenyl phosphate and triphenyl phosphate enhance adipogenesis and transcriptional activity of peroxisome proliferator activated receptor (Ppargamma) on the adipocyte protein 2 (aP2) promoter.* PLoS One, 2017. **12**(4): p. e0175855.
20. Kassotis, C.D., et al., *Characterization of Adipogenic Chemicals in Three Different Cell Culture Systems: Implications for Reproducibility Based on Cell Source and Handling.* Sci Rep, 2017. **7**: p. 42104.
21. Deziel, N.C., et al., *A case-control study of exposure to organophosphate flame retardants and risk of thyroid cancer in women.* BMC Cancer, 2018. **18**(1): p. 637.
22. Phillips, A.L., et al., *Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study.* Environ Int, 2018. **116**: p. 176-185.
23. Hoffman, K., et al., *High Exposure to Organophosphate Flame Retardants in Infants: Associations with Baby Products.* Environ Sci Technol, 2015. **49**(24): p. 14554-14559.
24. Butt, C.M., et al., *Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers.* Environ Sci Technol, 2014. **48**(17): p. 10432-8.
25. Butt, C.H., K; Chen, A; Lorenzo, A; Congleton, J; Stapleton, HM, *Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey.* Environment International, 2016. **94**: p. 627-34.
26. Agency, U.E., *Environmental risk evaluation report: Isopropylated triphenyl phosphate (CAS nos. 28108-99-8, 26967-76-0 & 68937-41-7)*. 2009, UK Environment Agency: Bristol, UK.