



Source: EPA Chemistry Dashboard

CAS RN 115-86-6

Substance Name Triphenyl phosphate (TPHP or TPP)

Uses

TPHP is used as an additive flame retardant in polymers, textiles, polyurethane foam, electronic circuit boards, photographic films, and building materials. It is also a plasticizer in PVC and may be present in PVC coatings on telephone, TV and computer cables and in PVC wallpaper [1-3]. It is a component of Firemaster® 550 used in polyurethane foams and has been detected in baby products [2, 4] other children's products, carpet pads, and plastic parts of LCD monitors [5]. TPHP is also used as a plasticizer and may be in clothing, textiles, cosmetics, and personal care products [6].

In manufacturers most recent reporting to U.S. Environmental Protection Agency (EPA), they reported that TPHP is a solvent in manufacturing of photographic film paper, plate, and photo chemicals [7]. Maximum concentration in consumer photographic supplies was reported to be <1% by weight. It is used as a flame retardant and plasticizer in plastic product manufacturing, and constitutes 60-90% by weight of unspecified consumer plastic and rubber products according to one manufacture. It is 60-90% by weight in some commercial lubricants and greases. Another manufacture reported 1-30% by weight of TPHP in plastic and rubber products and less than 1% in foam seating and bedding. Finally, it was reported to be used as a flame retardant in computer and electronic product manufacturing, textiles, apparel and leather manufacturing [7].

Manufacturing

Seven domestic sites reported manufacturing or import of TPHP in 2016. U.S. national production was given in ranges: 1-10 million pounds in 2012 and 2013, 10-50 million pounds in 2014, and 1-10 million pounds in 2015 [7]. This is considered high volume chemical production by EPA.

Toxicity

EPA classified TPHP as a high hazard for toxicity from repeated exposures [8]. Decreased body weight gain in adult rats was the most sensitive endpoint reported following repeated oral exposure; the no-observed-adverse-effect-level (NOAEL) was 70 mg/kg-day. At higher doses, increased liver weights, reproductive and fetal effects were observed [8].

TPHP appears to be active in reproductive tissue and other organs. Mice exposed to 300 mg/kg-day TPHP orally for 35 days had decreased testes weight, histopathological damage, decreased testicular testosterone levels, decreased expression of genes related to testosterone synthesis, and signs of oxidative stress in the liver [9]. *In vitro* testing shows that TPHP is a moderate androgen-receptor binder and can inhibit receptor function (testosterone-induced androgen-receptor-dependent activity) [8]. Significant estrogen receptor activity was observed in EPA's Endocrine Disruption Screening Program. TPHP was positive in 8 out of 16 estrogen receptor assays [10]. TPHP and its hydroxylated metabolites acted as estrogen receptor agonists in other *in vitro* studies [11, 12]. TPHP also may affect thyroid hormone regulation and synthesis. For example, TPHP affected thyroid development and function in the zebrafish [13].

Only limited human evidence of endocrine disruption is available. A study in Boston reported that men living in homes with higher TPHP in house dust had decreased sperm counts and altered hormone (prolactin) levels [14]. A more recent investigation in this same population of men did not find a consistent association between levels of TPHP's main urinary metabolite, diphenyl phosphate (DPHP, in urine and sperm count or other sperm parameters [15]. In a study of women undergoing IVF treatments in Connecticut, there was a significant trend detected between increasing DPHP metabolite in urine and decreasing frequency of fertilization, implantation, and pregnancy resulting from the in vitro fertilization (IVF) cycle [16]. A positive association between urinary concentrations of DPHP metabolite (specific gravity corrected) and increased serum levels of total thyroxine (TT4) were observed in a study of 51 adult office workers in the Boston Area in 2010-11 [17]. The association was primarily observed in women where high urinary DPHP was associated with a 0.91 µg/dL increase in mean TT4 levels compared to low DPHP. The association was present but not statistically significant in male participants. No association was found between urinary DPHP and serum levels of free thyroxine (fT4) total triiodothyronine (TT3), and thyroid stimulating hormone (TSH) [17]. No association was reported in a case-control study between TPHP metabolite (DPHP) level in urine and risk of papillary thyroid cancer in women [18].

There is also emerging evidence that TPHP may cause long-lasting metabolic disruption in rats exposed during fetal and nursing periods [19, 20]. Green et al., 2016, showed that developmental exposure to TPHP alone, caused accelerated onset of type 2 diabetes in a rat diabetes model and increased body fat later in life [20]. The very low dose used in this study (17 µg/rat-day or <0.5 mg/kg-day) was not associated with overt toxicity or weight change in treated dams or offspring at birth. It was equivalent to the dose of TPHP present in a rat study conducted by Patisaul et al. 2013, that observed metabolic disruption in offspring following developmental exposure to 1 mg/rat-day of Firemaster® 550 [19]. There is supporting mechanistic evidence that TPHP activates human peroxisome proliferator-activated receptor gamma (PPAR γ) and induces adipogenesis *in vitro*. [21-23]. PPAR γ is a master regulator of

adipogenesis during human development and a modulator of metabolism and insulin sensitivity. These studies suggest that TPHP may have a high hazard for developmental toxicity.

TPHP was identified as a chemical known to cause clinical neurotoxicity in adult humans in a review of industrial chemicals with potential for developmental neurotoxicity [24]. Investigators at the National Toxicology Program used cell-based *in vitro* assays and assays in rapidly developing whole organisms to screen for potential developmental neurotoxicity of a number of phosphate flame retardants [25-27]. TPHP had a more potent impact on larval development of the roundworm *C. elegans* than PBDE flame retardants and was a relatively strong inhibitor of mitochondrial activity in *in vitro* testing [26]. In zebrafish, both acute exposure and developmental exposure to TPHP produced behavioral changes in larvae [27]. The lowest observed effect levels (LOELs) for behavioral effects were 3-5 times lower than LOELs for overt toxicity in zebrafish. While behavior in the zebrafish assay is not directly predictive of effects in people it is a sensitive indicator of integrated nervous system function and possible low dose effects.

Exposure

TPHP is an additive flame retardant and plasticizer used in many everyday products and materials. It migrates out of computer monitors and TV sets [2] and has been measured at high levels in the dust on top of electronics [28]. It was found in surface wipes of 100% of cellphones and personal computers in a recent Chinese study; median levels were 228 pg/m² and 65 pg/m², respectively [29]. TPHP is a listed ingredient in nail polish and a recent biomonitoring study showed short-term spikes in human exposure following application of nail polish [30].

Because of its physical properties, TPHP that escapes from consumer products, either by emission or abrasion, is likely to end up in indoor dust. TPHP was detected at high levels in indoor dust in studies of homes in North Carolina, Boston, California, and Canada [31-35]. Maximum detected level was 1,800 µg/g dust. It has been detected in U.S. office and vehicle dust. [36]. TPHP has been measured in the indoor air of homes and public buildings in a number of countries. The maximum level reported was 100 ng/m³ [2]. Ambient air measurements of TPHP were collected over 6 week intervals in 2012 and 2013 in the Chicago, Illinois area. The geometric mean of multiple samplers ranged 0.17- 0.58 ng/m³ [37].

The average daily dietary intake of TPHP in 1982-1984 was estimated by the U.S. Food and Drug Administration (FDA) monitoring program for chemical contaminants in the U.S. food supply. Estimates were 4.4 ng/kg- day for 2 year olds, 0.8 ng/kg- day in adult females, and 1.6 ng/kg-day in adult males [38]. In more recent assessments, dietary surveys in Sweden and Belgium [39, 40] showed that TPHP was commonly detected in fats and oils, grains, baby food, meats and fish. In the Belgian study, dietary intake of TPHP for the typical adult was estimated to be 46.6 ng/kg -day. In the Swedish study [39], average adult daily intake was estimated as 9.7 ng/kg-day [40].

Diphenyl phosphate, a major metabolite of TPHP, has been found in urine at high frequency (>90%) in North American biomonitoring studies including Boston adults [41], New Jersey mothers and toddlers [42], California mothers and their children aged 2-70 months [43], North Carolina infants [44], and North

Carolina toddlers[35]. Levels of urinary DPHP measured in children were higher than their mothers [42, 43, 45] and were associated with TPHP in hand wipe samples [35]. Exposure was higher in children with more reported hand-to-mouth behaviors [42, 43]. Mean and median levels of DPHP in urine reported across these studies have been ≤ 3.2 ng/mL [46] with a maximum reported level of 140 ng/mL in children [42] and 657 ng/mL in adults [16].

The Centers for Disease Control and Prevention (CDC) added the diphenyl phosphate metabolite to the 2013-2014 survey of the National Health and Nutrition Examination Survey biomonitoring program. This is the first large representative study of DPHP in urine of U.S. residents. The survey didn't include toddlers but levels were higher in younger participants. Median and 95th percentile values were 1.70 and 13.0 ng/ml for 6-11 year old children, 1.44 and 7.94 ng/ml for 12-19 year old children and 0.72 and 5.43 for adults ≥ 20 years old. Asian participants had slightly lower levels and non-Hispanic black participants had slightly higher levels compared to Mexican Americans, non-Hispanic whites and all Hispanics. Total detection frequency was 92% and the maximum value reported was 193 ng/ml [47] [48].

TPHP has been measured up to 140 ng/g lipid in human breast milk in Asian and Swedish studies [49, 50]. TPHP was detected in 98% of hair samples and 74% of finger and toenail samples in a population of young adults in Indiana [51].

TPHP appears to be ubiquitous in the environment and has been detected in drinking water, river water, seawater, rainwater, snow, wastewater effluent, and ambient air [2, 8, 52-57].

Environmental Fate

Summary from National Library of Medicine, Hazardous Substances Database[38]

If released to air	<ul style="list-style-type: none"> • The vapor pressure indicates TPHP will exist in both the vapor and particulate phases in the atmosphere. • The half-life for TPHP in vapor-phase is estimated to be 12 hours. • Particulate-phase TPHP may undergo long-range transport before being removed from the atmosphere by wet and dry deposition.
If released to soil	<ul style="list-style-type: none"> • TPHP is expected to have slight mobility and to volatilize from moist soil surfaces although adsorption to soil is expected to attenuate volatilization. • Half-lives of 37 and 32 days under aerobic and anaerobic conditions, respectively, in a loamy sand suggest that biodegradation is an important environmental fate process in soil.
If released into water	<ul style="list-style-type: none"> • TPHP is not expected to adsorb to suspended solids and sediment. • Biodegradation, hydrolysis and volatilization from water surfaces are expected to be important environmental fate process in water. • Half-lives in river water were 2-4 days.

<p>Bioconcentration and bioaccumulation</p>	<ul style="list-style-type: none"> Bioconcentration factors ranging from 132 to 573 in fathead minnows and rainbow trout suggest that bioconcentration in aquatic organisms is high. A bioaccumulation factor for rainbow trout from a 24 hour short-term test was 2,590. Limited testing of fish from North America have shown levels of 0.1-1 µg/g THPH in muscle tissue.
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Physical-Chemical Properties of TPHP from EPA Chemistry Dashboard:

Chemical Properties	Average		Median		Range		Unit
	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	
LogP: Octanol-Water	4.59 (1)	4.03 (5)	-	4.12	4.59	2.67 to 4.70	-
Water Solubility	5.82e-06 (1)	2.06e-05 (4)	-	7.10E-06	5.82E-06	3.17e-06 to 6.52e-05	mol/L
Density	-	1.25 (2)	-	1.25	-	1.24 to 1.27	g/cm ³
Flash Point	-	213 (2)	-	213	-	202 to 224	°C
Melting Point	50.1 (8)	65.3 (4)	50	62.9	49.0 to 50.5	48.8 to 86.5	°C
Boiling Point	289 (4)	399 (5)	249	404	245 to 413	350 to 441	°C
Surface Tension	-	44.8 (2)	-	44.8	-	41.2 to 48.4	dyn/cm
Thermal Conductivity	-	236 (1)	-	-	-	-	mW/(m*K)
Vapor Pressure	6.28e-06 (1)	2.39e-05 (4)	-	4.60E-06	6.28E-06	1.24e-06 to 8.53e-05	mmHg
Viscosity	-	22.4 (1)	-	-	-	-	cP
LogKoa: Octanol-Air	-	10.8 (1)	-	-	-	-	-
Henry's Law	-	1.78e-06 (1)	-	-	-	-	atm-m ³ /mole
Index of Refraction	-	1.60 (1)	-	-	-	-	-
Molar Refractivity	-	87.7 (1)	-	-	-	-	cm ³
Molar Volume	-	258 (1)	-	-	-	-	cm ³
Polarizability	-	34.8 (1)	-	-	-	-	Å ³

Numbers in parentheses indicate the number of measurements or model predictions identified by EPA.

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