Ethanol, 2-chloro-, phosphate (3:1): Human health tier III assessment

10 March 2017

CAS Number: 115-96-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

For more detail on this program please visit: www.nicnas.gov.au

Disclaimer

Synopsis

The Tier II human health assessment of the chemical under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework determined that further work is required to evaluate the risk posed by the chemical ethanol, 2-chloro-, phosphate (3:1) (TCEP; CAS No 115-96-8) in household articles and particularly when used in toys. Therefore, a human health Tier III assessment was recommended.

This assessment indicated that the presence of TCEP in children’s toys can pose a risk for human health. However, the exposure intake estimates are assumed to be overestimates as shown by the Australian biomonitoring data. Therefore, the extent of the potential risk posed by the chemical in children’s toys cannot be reliably estimated and further information would be required to justify risk management measures. The use of TCEP is expected to decline due to existing international regulations. Therefore, no further risk management is recommended at present.

Quantitative risk assessment was conducted using a margin of exposure (MOE) approach to evaluate the potential health risks in children associated with exposure to TCEP via mouthing of toys. The estimated exposure intake due to mouthing was compared to the other intake sources based on publicly available estimates of daily exposure intakes. Additionally, the reverse dosimetry was used to estimate daily intakes of the chemicals in Australian children based on measured urine concentrations of TCEP.The human health Tier II IMAP report for the chemical is available at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1996 and contains detailed assessment information that remains valid (NICNAS).

New or updated information is included in the relevant sections of the Tier III human health report. The Tier II and Tier III reports for this chemical should be read together.

Rationale for Tier III Assessment

Ethanol, 2-chloro-, phosphate (3:1) (TCEP) is a flame retardant plasticiser, commonly used in various household applications including paints and coatings, furniture, textiles, insulation and polyurethane foam. The chemical has been measured in several consumer products such as mattresses, furniture, automobile seating and in certain infant and toddler products including toys (Stapleton et al., 2009; 2011, 2012; Canada Gazette, 2014; Washington State, 2014; TERA, 2015; Danish EPA, 2014; 2015; 2016).

The chemical is hazardous to human health. It is a suspected carcinogen (Carc. Cat. 3; R40) and may impair fertility (Repr. Cat. 2; R60) (Safe Work Australia). The mechanisms inducing cancer are not fully understood. However, based on the mainly

negative genotoxicity studies (NICNAS), the TCEP-induced tumours observed in rodent studies (NICNAS) are expected to be related to non-genotoxic mechanisms of carcinogenicity.

The chemical TCEP has toxic effects in the kidney, liver and brain following repeated oral treatments in experimental animals (EU RAR, 2009; ATSDR, 2012; US EPA, 2015a; 2015b; NICNAS).

The chemical may be released from various products due to its migration to the surface or via matrix decomposition, aging or mechanical action. Flame retardants are present in airborne and settled dust within home or other indoor environments (Makinen et al, 2009; Cao et al., 2014; Yang et al., 2014; Canbaz et al., 2016; Brandsma et al., 2014; Keimowitz et al., 2016; He et al., 2015; 2016; Wu et al., 2016). Therefore, exposure may occur via inhalation, dermal or oral (hand-to-mouth, ingestion of settled dust or mouthing activities) routes. Children are expected to have highest intakes, due to having lowest body weights and highest frequency of hand-to-mouth activities as well as age specific activities including mouthing of products. Children are also expected to have highest percentages of time spent in indoor environments such as homes, schools, day-care, public and commercial buildings and in vehicles, where exposure to TCEP is most likely (Isaacs et al., 2014; US EPA, 2015a).

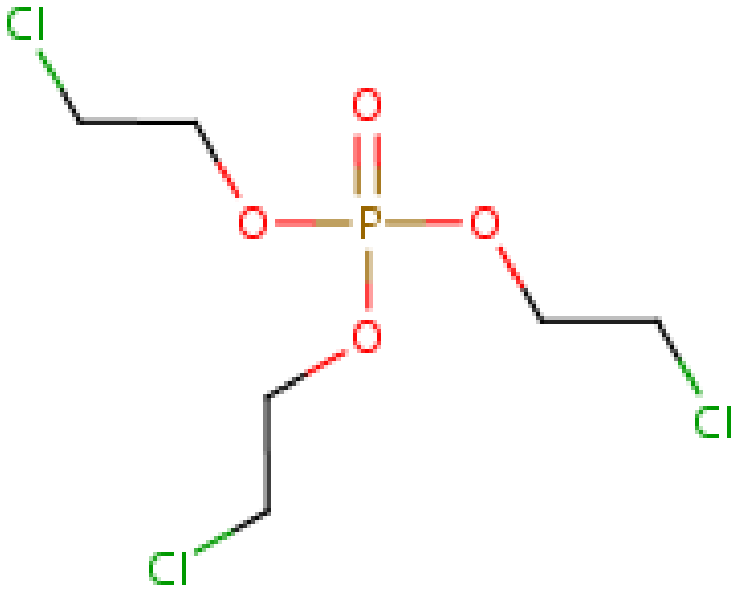
The chemical TCEP or its metabolite bis(2-chloroethyl) phosphate (BCEP) has been detected in the human serum (Li et al., 2015) and urine samples demonstrating the bioavailability and absorption of TCEP in humans (TERA, 2015). The TCEP was measured in urine samples in Australia, with the chemical detected in 35 % of samples from children up to three years of age, but not in samples from older children or adults (van den Eede et al., 2015).

The use of TCEP has been restricted in various products overseas, including in children's toys (See ***Restrictions***). Due to the international restrictions, the commercial use of TCEP as a flame retardant has declined; however, its use in products including children's toys is not restricted in several countries including Australia and therefore the chemical may present a health risk for consumers in Australia.

The scope of the Tier III assessment is to determine if mouthing of products containing TCEP, such as children's toys, is a significant exposure route in Australian infants and toddlers and if this exposure route poses a significant risk for human health.

Chemical Identity

Synonyms	tris (2-chloroethyl) phosphate TCEP 2-chloroethanol phosphate Celluflex Niax Flame retardant 3CF
Structural Formula	



Molecular Formula	C6H12C13O4P
Molecular Weight (g/mol)	285.4
Appearance and Odour (where available)	A clear liquid with a light odour
SMILES	C(C1)COP(=O)(OCCC1)OCCC1

Import, Manufacture and Use

Australian

See the IMAP Tier II Human Health Hazard assessment for more detailed information.

International

The chemical TCEP has been widely used in polyurethanes, polyacrylates, and polyester resins. In general, to achieve appropriate flame retardant effects, the loading rates of the chemical in flexible foams are between 2.5 and 14 % (EU RAR, 2009). The chemical has uses in the building (e.g. insulation), furniture and textile (e.g. as back-coatings for carpets and upholstery) industries, in aircrafts, cars and trains, as well as in professional paints, varnishes and lacquers (EU RAR, 2009; SCHER, 2012; CDR, 2012; Environment & Health Canada, 2009).

The production and use of TCEP has declined and been progressively replaced by other flame retardants such as tris(1-chloro-2-propyl) phosphate (TCIPP; CAS No 13674-84-5) (WHO, 1998; US EPA, 2015a; Schreder et al. 2016). The chemical TCEP is also a known impurity in the commercial 2,2-bis(chloromethyl)-propane-1,3-diyltetrakis(2-chloroethyl) bisphosphate (V6 mixture; CAS No 38051-10-4) at concentrations of 4.5-7 % (Fang et al, 2013; US EPA, 2015b).

See the IMAP Tier II Human Health Hazard assessment for more detailed information.

Restrictions

Australian

No known restrictions have been identified.

International

The Government of Canada has listed the chemical in Schedule 2 of the Canada Consumer Product Safety Act: “Products that are made, in whole or in part, of polyurethane foam that contains tris (2-chloroethyl) phosphate and that are intended for a child under three years of age” (Canada Gazette, 2014).

In Europe, the Toy Safety Directive currently limits the presence of TCEP in toys intended for children aged under 36 months and in toys that could be put in their mouth to 5 mg/kg as a ‘detection limit of a sufficiently sensitive analytical method’ (EC Directive 2009/48/EC, as amended June 2014). This Directive came into force on 21 December 2015.

In the United States of America (USA), restrictions of TCEP in children’s products, upholstered furniture, the manufacture and sale of children's products, upholstered residential furniture, residential textiles, or mattresses have been proposed or adopted in multiple states including Massachusetts, Washington, Alaska, Maryland, New York, Connecticut, Delaware, Maine, Minnesota, North Carolina, Rhode Island and Tennessee (Safer States).

Public Exposure

In this assessment, public exposure to TCEP is presented as:

- estimates of exposure intake (oral route) for the use of the chemical in children’s toys;
- a summary of main findings from international assessments of exposure intakes (various routes) for the use of the chemical in different products used in infant and children’s articles, in indoor air and dust, and in drinking water and food; and
- estimates of exposure intake from biomonitoring data.

The exposure intakes are presented to allow the characterisation of the risks associated with the use of TCEP.

Exposure intake from children’s toys

While TCEP is regulated in children’s toys in certain countries, polyurethane toys potentially containing TCEP may still be available in Australia. Three different methods of intake estimations from toys are presented here: foam ingestion, migration, and solubility. The exposure estimates from mouthing of toys are calculated for typical and reasonable worst-case exposure scenarios using these three methods.

Foam ingestion method

This method is based on the potential ingestion of polyurethane foam containing TCEP following mouthing of the toys.

The chemical TCEP was measured in one out of five toys sampled in a Danish study (as cited in EU RAR, 2009) conducted prior to TCEP restrictions. The chemical was detected in a soft cube made of textile, plastic and foam rubber with the core consisting of polyurethane foam. The TCEP levels in the polyurethane foam cube were reported to be 3300, 5200 or 6500 mg/kg, while the textile TCEP content was 160 mg/kg (EU RAR, 2009; SCHER, 2012). In a more recent Canadian assessment (Canada Gazette, 2014), TCEP was detected in children’s soft polyurethane foam book at a concentration of 3800 mg/kg. There

is no available information on the concentration of TCEP in toys in Australia, but the overseas data is considered representative for the purpose of estimating the exposure intake of children mouthing toys containing TCEP.

The calculations in this method were based on the assumption by the Danish Environmental Protection Agency (EPA) as reported in the EU RAR (2009) that a 3-month old baby plays with a polyurethane foam cube for 90 days, during which the cube is sucked intensively. The following assumptions were also used:

- cumulative amount of foam ingested during 90 days was 50 g (EU RAR, 2009). Based on this information, this assessment estimated ingestion of approximately 0.55 g of foam per day);
- intermediate TCEP concentration in foam of 5200 µg/g from the Danish study (as reported in EU RAR, 2009 and SCHER, 2012);
- a 50 % release rate of TCEP from the foam (EU RAR, 2009); and
- the TCEP's bioavailability via the oral route of 100 % since the chemical is expected to be efficiently absorbed orally (EU RAR, 2009; TERA, 2015; NICNAS).

The exposure intake (foam ingestion), in µg/kg bw/day, was estimated as follows:

$$\text{Exposure intake (foam ingestion)} = [RF \times C \times A \times B_{oral}] / BW$$

Where:

RF = Release factor

C = Concentration of TCEP in foam ingested, µg/g

A = Amount of foam ingested per day, g/day

B_{oral} = Bioavailability via oral route

BW = Body weight

The age-groups, and age-specific default values for body weights and exposure duration of daily mouthing of toys are shown in Table 1. The exposure intake was not calculated for the 0-3 month age group since minimal exposure duration of mouthing is reported for this group.

Table 1: Age-specific average default values used for body weights (BW) and for average and maximum (in brackets) exposure duration (ED) of daily mouthing of toys (based on enHealth, 2012).

Age group (months)	BW (kg)	ED (min/day)
0 - 3	4.8	0.25 (1)
3 - 6	6.9	28 (155)
6 - 9	8.1	39 (226)
9 - 12	8.9	23 (65)

Age group (years)	BW (kg)	ED (min/day)
1-2	11	15 (64)
2-3	15	12 (125)
3-6	24	5 (65)

Estimations were made for exposure intake of children of various age groups using the assumptions and equation above (see Table 2; **Exposure estimates from the three methods**).

The assumption of 0.55 g of foam ingested per day was reported for ages between 3 to 6 months (EU RAR, 2009). The same daily ingestion rate was used for all ages, except for 0-3 months when no sufficient mouthing is expected and the foam ingestion would be negligible. It is noted that the time children spent sucking toys, peaks at ages 6 to 9 months (enHealth, 2012; Table 1), and the biting behaviour is most common in children aged between 6 to 24 months (SCHER, 2016).

Migration method

This method is based on the potential migration of TCEP into the saliva following mouthing of toys. The TCEP is subsequently swallowed with saliva and also absorbed through the buccal mucosa.

The amount of TCEP released is determined by the amount of time children spend with the product in their mouth and the migration rate of TCEP from the toy. No information is available for the migration of TCEP to saliva. Migration rate to artificial, sweat-like solutions has been measured for chlorinated phosphoester flame retardants. Based on a Danish EPA report, the TCEP migration rate to artificial sweat from a product containing TCEP was reported to be up to 620 mg/m^2 during a 3-hour test period (62 µg/cm^2/3hr = 20.6 µg/cm^2/hr) (Danish EPA, 2016). This approach was used to estimate the exposure for children to two chlorinated phosphoester flame retardants in a recent report (Environment & Health Canada, 2016).

Due to the lack of migration studies of TCEP into saliva, this assessment assumes that migration rate of the chemical into artificial sweat is representative. The following assumptions were also used:

- the surface area of a child's open mouth and the surface of an article available for mouthing at any one time is approximately 20 cm^2 (Environment & Health Canada, 2016);
- migration rate of TCEP to saliva is 20.6 µg/cm^2/hr (Danish EPA, 2016);
- mouthing frequency occurs equally for both plastic and polyurethane foams, hence, a relative mouthing frequency (RMF) of 50 % (or 0.5) for foam toys; and
- the TCEP's bioavailability via the oral route is 100 % since the chemical is expected to be efficiently absorbed orally (EU RAR, 2009; TERA, 2015; NICNAS).

The exposure intake (migration), in µg/kg bw/day, was estimated as follows:

$$\text{Exposure intake (migration)} = [SA \times M \times ED \times RMF \times CF \times B_{oral}] / BW$$

Where:

SA = Surface area of direct mouthing, cm2

M = Migration rate, µg/cm2/hr

ED = Exposure duration, hr/day

RMF = Relative mouthing frequency

CF = Conversion factor of 1/60 (min/day to hr/day)

B_{oral} = Bioavailability via oral route

BW = Body weight

Estimations were made for exposure intake of children of various age groups using the assumptions and equation above (see **Exposure estimates from the three methods**). The age-groups, and age-specific default values for body weights and exposure duration of daily mouthing of toys are shown in Table 1.

Solubility method

This method is based on the expectation that the solubility of TCEP in water is the same as its solubility in saliva, and that the chemical contained in polyurethane in toys migrates to the saliva. This model was developed by the US Environmental Protection Agency (US EPA)'s Voluntary Children's Chemical Evaluation Program for another flame retardant (Environment & Health Canada, 2009).

The water solubility used in the equation above is 7000 µg/mL (Hou et al., 2016). The unstimulated salivary flow rate in children's mouth is assumed to be 0.22 mL/min measured from a 5-year old child (Bretz et al., 2001; Environment & Health Canada, 2009). The default value of 0.038 used for fractional rate extraction by saliva has been used for other halogenated flame retardants (as referenced in Environment & Health Canada, 2016).

The following assumptions were also used:

- the TCEP's bioavailability via the oral route is 100 % since the chemical is expected to be efficiently absorbed orally (EU RAR, 2009; TERA, 2015; NICNAS); and
- the relative mouthing frequency (RMF) of 0.5 for foam toys (see **Migration method**).

The exposure intake (solubility), in µg/kg bw/day, was estimated as follows:

$$\text{Exposure intake (solubility)} = [WS \times Vs \times CF \times FR \times B_{oral} \times ED \times RMF]/ BW$$

Where:

WS = Water solubility of TCEP, µg/mL

Vs = Salivary flow rate

FR = Fractional rate extraction by saliva

B_{oral} = Bioavailability via oral route

ED = Exposure duration (min/day)

RMF = Relative mouthing frequency

BW = Body weight

Estimations were made for exposure intake of children of various age groups using the assumptions and equation above (see Table 2, **Exposure estimates from the three methods**). The age-groups, and age-specific default values for body weights and exposure duration of daily mouthing of toys are shown in Table 1.

Exposure estimates from the three methods

The estimated exposure intakes from the foam ingestion, migration, and solubility methods are shown in Table 2. The calculations are presented as typical (using average mouthing exposure duration) and reasonable worst-case (using maximum mouthing exposure duration) values.

Table 2: Typical and reasonable worst-case (in brackets) exposure intakes (µg/kg bw/day) from mouthing toys for children of different age groups using three different methods.

Age group (months)	Ingestion	Migration	Solubility
0 – 3	negligible	0.18 (0.72)	1.5 (6.1)
3 – 6	207	14 (77)	119 (657)
6 – 9	177	16 (96)	141 (816)
9 – 12	161	9 (25)	76 (214)
Age group (years)	**Ingestion**	**Migration**	**Solubility**
1-2	130	4.7 (20)	40 (170)
2-3	95	2.7 (29)	23 (244)
3-6	60	0.72 (8.9)	6.1 (76)
Average (0-6 years)	138	6.8 (37)	58 (312)

The estimations presented in Table 2 show a high variability of exposure intakes from the three different methods and assumptions used. Therefore, it is not possible to provide reliable estimates of TCEP exposure of children mouthing toys. Similarly, the Scientific Committee on Health and Environmental Risks (SCHER, 2012) concluded in their assessment of TCEP in toys that “the database is not appropriate to derive a reliable estimate”.

The uncertainties in the exposure assessment for this scenario are discussed in the context of the risk characterisation (see **Uncertainties in the risk assessment**).

Exposure intake from children's products, indoor air, indoor dust, food, and drinking water

The information presented here is not a full literature review, but rather summarises the main findings from international sources of exposure intakes of TCEP in different products used in infant and children's articles, in indoor air and dust, and in food and drinking water.

Concentrations determined in various children's products (other than toys)

The chemical has also been measured in various infant products such as high chairs, bath mats, car seats, nursing pillows, carriers (Stapleton et al., 2011; Washington State, 2014; Danish EPA, 2015; 2016), sofas (Stapleton et al., 2009; 2012), and camping tents (Keller et al., 2014). In a Danish Consumer Council test of children's articles, TCEP was measured in children's car seats, baby slings and prams (Danish EPA, 2016). The TCEP levels ranged between 41-840 mg/kg. In the USA market, TCEP was detected in concentrations over 1000 mg/kg foam in car seats, changing pads, sleep positioners, portable mattresses, nursing pillows, baby carriers, rocking chairs, high chairs, infant bath mats, and baby walkers (Stapleton et al., 2011; TERA, 2015).

Concentrations determined in indoor air

Due to its physicochemical properties, TCEP can be classified as semi-volatile organic compound, and therefore is not expected to be abundantly present in a gaseous state (the maximum saturated airborne concentration is estimated to be 940 $\mu g/m^3$ (TERA, 2015)). The chemical TCEP is typically classified as "additive flame retardant" and is blended evenly into the foam, but remains unbound. The internal structure of the foam however acts as a barrier to migration of the chemical to the surface from which it can be volatilised. The chemical TCEP has been shown to migrate to the environment, either by migration from the products and adsorption to particulates or via matrix decomposition, aging or release. The chemical is also shown to be emitted from electrical and electronic products (Malmgren-Hansen et al., 2003; TERA, 2015). Other likely sources of TCEP concentrations in indoor air are: polyurethane foams; upholstery; furniture; and textiles (ATSDR, 2012; CPSC, 2013).

The concentrations of TCEP measured in indoor air ranged from not detected to 870 ng/m^3 in various microenvironments (TERA, 2015). The indoor air concentrations of TCEP measured in Japan and Sweden ranged from non-detectable to 136 ng/m^3 and 1-115 ng/m^3, respectively (TERA, 2015).

Concentrations determined in indoor dust

The high octanol: air equilibrium partitioning coefficient (Koa) and low vapour pressure of TCEP favour partitioning to solid organic matrices like dust. The TCEP has been measured in dust and particulate matter in various indoor locations in the range of non-detectable to 2300 mg/kg (TERA, 2015). Recently, TCEP was measured in dust collected from Australian homes, schools, cars and mattresses in the range of non-detectable to 62 mg/kg (Harrad et al., 2016). The median levels in car and living room dust were 2 and 0.6 mg/kg, respectively.

The levels of TCEP are variable and differ in different locations. Highest concentrations are generally found in cars and public places like schools (TERA, 2015). In general, the concentrations of flame retardants in indoor air are considerably higher than the outdoor concentrations, supporting the role of indoor environments as an important exposure source.

Concentrations in food and drinking water

Exposure to TCEP may also occur via water and food, although these sources, especially food, are considered a minor contribution overall. No information is available on the TCEP concentrations in Australian drinking water or food items.

Conventional water treatment may not be effective in removing TCEP from drinking water (TERA, 2015). In Canada, the TCEP concentrations in drinking water ranged from non-detectable to 52 ng/L (Environment & Health Canada, 2009). In the USA, the highest concentrations of TCEP found in two drinking water sites during a US Geological Survey (USGS), was approximately 66

ng/L (0.066 parts per billion). In another study in the USA, TCEP was detected in public drinking water with the maximum concentration of 20 ng/L (SPSC, 2013).

Levels of TCEP were detected in various food items in a market basket study performed by the United States (US) Food and Drug Administration. The mean concentrations ranged between maximum of 29 µg/kg in oriental noodle soup to below detection in various other items (as reported in Environment & Health Canada, 2009). In a Swedish market basket study performed in 2015, median TCEP concentrations ranged from 1 µg/kg in fats/oils, 0.45 µg/kg (fresh weight) in vegetables to below detection (Swedish EPA, 2016; Poma et al, 2017). The levels of TCEP were also measurable in certain infant and toddler foods in the USA (Environment & Health Canada, 2009). The TCEP concentrations in fish range from not detected to 90 µg/kg (Environment & Health Canada, 2009). The suggested sources of TCEP concentrations in food may include the wrapping material used in food packaging and the plant uptake from soil (TERA, 2015), and could also be from contamination in processing plants.

Chlorinated organophosphate flame retardants have also been measured in mothers milk (Sundkvist et al, 2010). Concentrations of TCEP were detected in 3-8% of human breast milk samples of women from Vietnam, Philippines, and Japan (Kim et al, 2014). The concentrations ranged from non-detectable to 512 ng/g lipid (median 0.14-42 ng/g lipid, depending on country measured). However, sufficient information was not available to determine the source of exposure from mother's milk.

Summary of exposure estimates from various sources other than mouthing

The exposure routes and sources commonly identified for chlorinated organophosphate flame retardants include: oral exposure via hand-to-mouth transfer of settled dust on surfaces, inhalation exposure including incidental ingestion of inhaled dust, dermal exposure through contact with products or dust containing TCEP, and oral exposure to TCEP in food and drinking water, including from settled indoor dust particles (Environment & Health Canada, 2009; 2016; EU RAR, 2009; SCHER, 2012; Danish EPA, 2014; TERA, 2015; US EPA, 2015a).

The exposure estimates from various sources with the identified routes are shown in Table 3. These values were derived from existing international exposure estimates for the purpose of making a comparison. Both EU RAR (2009) and Environment & Health Canada (2009) concluded that mouthing was a significant route for infants and young children with the mouthing expected to contribute to over 90 % of the total exposure. However, other routes of exposure including dermal contact with products containing polyurethane foam (like mattresses, car seats etc.) have also gained attention as potentially significant exposure route for children (Danish EPA, 2015; Environment & Health Canada, 2016).

Table 3: Potential exposure intake (µg/kg bw/day) of TCEP via various routes as assessed by other international agencies.

	Health Canada, 2009				**EU RAR, 2009[a]**		
	Infant (0-6 months)	**Toddler (6 months -4 years)**	**Children (5-11 years)**	**Adults**	**Infant (3-6 months)[b]**	**Toddler (1-3 years)**	**Adults**
Drinking water	0.006	0.002	0.002	0.001	NA[c]	0.007-0.01	0.03-1.4
Food	0	0.009	0.004	0.002	NA	NA	NA
Hand-to-mouth	0.2	0.3	0.09	0.02	NA	0.2	0.003

(dust)							
Indoor air	0.09	0.2	0.2	0.008	NA	NA	NA
Dermal dust	0.36	0.27	0.25	0.25	NA	0.018	NA
Dermal contact	2	1	0.5	0.5	NA	10	3.9
Total intake	2.7	1.8	1.1	0.78	NA	10.2	4.3

a) The estimated 99th percentile as reported in European Union Risk Assessment Report (EU RAR, 2009) is listed for uptake values when available.

b) Only mouthing was estimated for infants between 3-6 months of age.

c) NA = Exposure was not estimated.

In addition to the international agencies, scientific research papers have estimated human exposure intakes via dust ingestion, inhalation, and dermal contact (van den Eede et al., 2011; Kim et al., 2013; Abdallah & Covaci, 2014; Cequier et al., 2014; Tajima et al., 2014; Brommer & Harrad, 2015; He et al., 2015; 2016; Hou et al., 2016; Schreder et al., 2016; Wu et al., 2016). The estimated exposure intakes between the studies are highly variable for each route. The variability is assumed to be due to differences in the use of consumer products, frequency of dust cleaning as well as regulations in indoor materials in different countries (Hou et al., 2016).

The estimated median exposure intake in children and toddlers (body weights used varying between 12 – 20 kg) via dust ingestion was 0.15 – 16.1 ng/kg bw/day depending on the study (van den Eede et al., 2011; Kim et al., 2013; Abdallah & Covaci, 2014; Cequier et al., 2014; Tajima et al., 2014; Brommer & Harrad, 2015; He et al., 2015; Hou et al., 2016; Schreder et al., 2016; Wu et al.,2016). In infants (5 kg body weight), the estimated mean exposure intake via dust ingestion was 161 ng/kg bw/day (He et al., 2016).

In a recent study in USA, the estimated median exposure intake in children via inhalation was 116 ng TCEP/day which corresponds to 5.8 ng/kg bw/day if 20 kg body weight is used (Schreder et al., 2016). In another study in Norway, the inhalation exposure intake in children (body weights not specified) was 0.91 ng/kg bw/day (Cequier et al., 2014).

The estimated daily intake in children (body weights not specified) via dermal contact of dust was estimated to be 1.6 ng/kg bw/day (Cequier et al., 2014).

In a recent Swedish market basket 2015 study (Swedish EPA, 2016), the estimated total TCEP intake from various food categories was estimated to be 6.0 ng/kg bw/day in adults (mean body weight of 67.2 kg).

Exposure intake from biomonitoring data

Biomonitoring data

Biomonitoring data for a particular chemical or its metabolites represent exposure to the chemical from all sources and pathways. The metabolism of TCEP in humans has not been fully evaluated and therefore, the best biomarkers for TCEP exposure in humans are unknown. The quantitative measurement is also challenging with the methods still under development (Petropoulou et al., 2016). These challenges are demonstrated by divergent findings in recent studies. The in vitro studies suggest that TCEP may not be effectively metabolised into hydrolytic metabolites like bis(2-chloroethyl)phosphate (BCEP) by human liver enzymes (Van den Eede et al., 2013). However, in urine samples (ex vivo), the chemical was enzymatically hydrolysed to BCEP, with BCEP concentrations increasing with duration of hydrolysis (Petropoulou et al., 2016). Therefore, the limited biomonitoring studies have been measuring either the parent TCEP or the proposed metabolite BCEP.

The levels of TCEP were recently measured in urine samples obtained from a community-based pathology laboratory from Queensland in Australia (van den Eede et al., 2015). Two separate sampling campaigns were undertaken in the following periods: (1) from November 2010 to March 2011; and (2) November 2012 to November 2013. The levels of TCEP were detected (method detection limit (MDL) <0.5 ng/mL) in 35 % of samples from children 0-3 years old, but not in samples from older children or adults. The maximum reported concentration in urine was 24 µg/L. Based on the scatter blot (Supplemental material; van den Eede et al., 2015) of urine samples with detectable TCEP levels, the median level detected was estimated to be 1 µg/L. This supports the estimated higher exposure in younger children. The MDL for metabolite BCEP was >3 ng/mL and was not measured (van den Eede et al., 2015).

The TCEP metabolite, BCEP, has been detected in urine samples of adults in the USA (Dodson et al., 2014; Petropoulou et al., 2016). The levels of BCEP were detected in 75 % of urine samples (n=16; detection limit 0.1 ng/mL). The median concentration of BCEP in urine was 0.63 ng/mL and the maximum concentration detected was 2.1 ng/mL (Dodson et al., 2014). In another study, using a different quantitation method, BCEP was detected in all urine samples (n=13; detection limit 0.1 ng/mL) with the median level detected at 1.3 ng/mL and the maximum level detected at 15 ng/mL (Petropoulou et al., 2016). The chemical BCEP, was detected in 65 % of urine samples (n=312; detection limit 0.1 ng/mL) from children between 22 and 80 months old in Germany (Fromme et al., 2014). The median concentration of BCEP in urine was 0.2 ng/mL and the maximum concentration detected was 13.1 ng/mL (Fromme et al., 2014).

The levels of TCEP were below the detection limit in serum samples of 50 adults in the USA, while the chemical was detected in 68, 20, or 8 % of hair, fingernail or toenail samples, respectively (Liu et al., 2016). The authors concluded that the lack of TCEP detection in serum is expected to be due to rapid metabolism and excretion of the chemical.

The analytical approaches and uncertainties associated with biomonitoring data limits their use in exposure and human health risk assessments (Albertini et al., 2006). It is not possible to determine the relative contribution of different exposure routes directly from population biomonitoring data. For this reason, modelling is most suitable. However, population biomonitoring data are useful in determining whether the exposures calculated through modelling are within the observed range of exposure, and their magnitude compared with the integrated exposure of the population.

Exposure estimates using reverse dosimetry

Reverse dosimetry was used to estimate daily intakes based on urine concentrations of TCEP.

The exposure intake (reverse dosimetry), in µg/kg bw/day, was estimated as follows:

Exposure intake (reverse dosimetry) = Cu × Vu/FUE × BW

Where:

Cu = Concentration of TCEP detected in urine, µg/L

Vu = Total daily urine volume, L/day

FUE = Fractional urine excretion

BW = body weight of a toddler age 0-3 years

For the urine concentrations, the results from sampling campaign 1 in a previously described study (van den Eede et al., 2015) were used. The following parameters were also used:

- the total daily urine volume is 0.7 L/day for toddlers (Environment and Health Canada, 2016);

- it is assumed that TCEP is minimally metabolised and excreted mainly unmetabolised. Approximately 75 % of radiolabelled chemical was excreted in the urine within the first 24 hours and 90 % within 96 hours in rodents (NICNAS; TERA, 2015). The results from the in vitro metabolism study using human liver preparations suggested that approximately 40 % of TCEP is metabolised into BCEP; hence, 60 % would be expected to be excreted as unmetabolised TCEP (van den Eede et al., 2013). Therefore, the FUE, the proportion of incomplete TCEP excretion, was estimated from the TCEP level excreted in urine (75 %), and the unmetabolised TCEP level (60 %); and

- a toddler body weight of 15 kg (enHealth, 2012).

Using the equation and parameter assumptions described above, the estimated median and maximum daily intakes in toddlers (0-5 years) were 0.1 and 2.5 µg/kg bw/day, respectively.

The worst-case TCEP exposure values of children mouthing toys, calculated using three different methods (Table 2), are greater than the calculated worst-case intake from biomonitoring information due to the significantly conservative assumptions used. The uncertainties in the exposure assessment for this scenario are discussed in the context of the risk characterisation (see **Uncertainties in the risk assessment**).

Health Hazard Information

The critical health effects of TCEP for risk characterisation include systemic long-term effects and systemic acute effects (NICNAS). The chemical TCEP is a suspected carcinogen (Carc. Cat. 3; R40) and may impair fertility (Repr. Cat. 2; R60) (Safe Work Australia). In addition, following repeated oral treatments in experimental animals, TCEP has toxic effects on the kidney, liver and brain (EU RAR, 2009; ATSDR, 2012; US EPA, 2015a; 2015b; NICNAS).

The chemical TCEP induces the formation of benign and malignant tumours at various sites in experimental animals. Benign kidney neoplasms are most commonly reported and have been observed in both rats and mice and in both sexes (EU RAR, 2009; NICNAS). The TCEP-associated responses observed in kidneys are not malignant and appear to be restricted to hyperplasia and benign tumours (adenomas). However, it is accepted that adenoma and carcinoma of the renal tubule constitute a morphological continuum and the renal adenomas may represent an early stage of the development of a carcinoma and are considered reasonable evidence of carcinogenic activity.

The mechanism of TCEP induction of tumours is unknown. As there is no relevant evidence for mutagenicity of TCEP, for the risk assessment, a threshold mode-of-action has been used to assess the carcinogenicity risk of TCEP (EU RAR, 2009). A number of non-genotoxic chemicals can induce of renal cell tumours through a process involving prolonged renal tubule cell injury coupled with regenerative cell proliferation (IARC, 1997). Two separate mechanisms have been proposed: (1) a regenerative response to chemically induced cytotoxicity that elicit compensatory cell proliferation; or (2) a regenerative response not dependent on direct chemical cytotoxicity related to impaired physiological process such as α2u-globulin nephropathy with associated renal carcinogenesis. Although more common in male rats, kidney tumours were also observed in female rats and in mice, following TCEP exposure. Neoplasia was also observed in other organs (EU RAR, 2009). Therefore, the mechanism is not expected to be related to α2u-globulin nephropathy that is specific to male rats (IARC, 1999), but rather to cytotoxicity with compensatory cell proliferation. It has been suggested that the observations of non-neoplastic lesions in kidney and other organs may be considered relevant for the assessment of carcinogenicity risks due to TCEP exposure (EU RAR, 2009).

A lowest observed adverse effect level (LOAEL) of 12 mg/kg bw/day has been reported for kidney lesions in chronic oral toxicity study in mice (NICNAS). The Scl:ddY mice were fed with a commercial diet containing approximately 0.012, 0.06, 0.3, and 1.5 % (equivalent to 12, 60, 300 and 1500 mg/kg bw/day, calculated on an assumed body weight of 20 g and food consumption of 10 % body weight/day) TCEP (purity 98 %) over a period of 18 months (EU RAR, 2009). Hyperplasia and hypertrophy of the urinary tubule epithelium together with enlarged nuclei, abnormal division, degeneration and necrosis were reported in kidneys of mice at dose of 12 mg/kg bw/day. However, no quantitative information on frequency of these microscopic findings in the kidney was reported, and therefore, the adversity of these effects could not be evaluated. Increases in renal cell adenomas and carcinomas as well as hepatocellular adenomas and carcinomas were reported at two highest does. A LOAEL of 44 mg/kg bw/day for dose dependent increases in renal tubular hyperplasia and adenomas (increased incidence compared to experimental and historical controls) was reported in F344/N rats administered TCEP by gavage for five days per week up to 103 weeks (NTP 1991; Matthews et al., 1993; NICNAS). A no observed adverse effect level (NOAEL) was not established in this study. This LOAEL for histopathological effects in kidneys is supported by a chronic exposure study with increased kidney weights observed at 44 mg/kg bw/day in female F344/N rats administered with TCEP by gavage for 16 weeks. In two 90-day oral toxicity studies in rats, a NOAEL of 22 or 22-30 mg/kg bw/day based on increased relative liver and kidney weights were

reported (NICNAS). With use of an adjustment factor of 3 for use of the LOAEL in place of a NOAEL, these two NOAELs based on organ weight changes, support the LOAEL of 44 mg/kg bw/day reported for neoplastic adenomas and tubular hyperplasia as well as organ weight changes. Therefore the LOAEL of 44 mg/kg bw/day is used for the present risk assessment.

Public Risk Characterisation

Methodology

A margin of exposure (MOE) methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB, 2003). The risk characterisation is conducted by comparing quantitative exposure information with a NOAEL selected from appropriate animal studies and deriving an MOE as follows:

1. Identification of critical health effect(s).
2. Identification of the most appropriate/reliable NOAEL for the critical health effect(s). If NOAEL was not identified, a LOAEL can also be used but will require a higher margin of safety.
3. Comparison of the estimated or measured dose or exposure (Dose) with the appropriate/reliable NOAEL to provide an MOE calculation (MOE = NOAEL (LOAEL)/Dose).
4. Evaluation as to whether the MOE obtained by this method indicates a health concern for the human population under consideration, taking into account relevant safety factors.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. Higher MOE values indicate lower risk of potential adverse effects. To decide whether the MOE is of sufficient magnitude, expert judgement is required. Such judgements are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability. With the interspecies and intraspecies assessment factors of 10, the acceptable MOE for NOAEL-based assessment is 100 or greater, based on a NOAEL from a 90-day study. If a LOAEL instead of a NOAEL is used, additional factor of 3 is appropriate (ECETOC, 2003). Therefore, the acceptable MOE for LOAEL-based assessment is 300 or greater, based on a 90-day study.

In this assessment, the MOE methodology was used for characterising the risks from TCEP exposure due to mouthing of toys containing TCEP.

Risk estimate related to the mouthing of toys containing TCEP

Based on the exposure estimates from various sources, mouthing of toys containing TCEP is considered the main source of exposure in infants and toddlers (>90 % of total exposure). As there is currently no reliable way to estimate the exposure intake via mouthing, the exposure intakes were derived for mouthing using all available and recently used methods: solubility, migration and ingestion (Table 2). Where relevant, the MOEs were calculated for the estimated average and worst case intakes using the LOAEL of 44 mg/kg bw/day. The average exposure intake was calculated using the mean exposure duration (estimated mouthing times for toys as shown in Table 1; enHealth, 2012) while worst case scenario assumed maximal exposure duration (estimated mouthing times for toys as shown in Table 1 in brackets; enHealth, 2012).

As described above, due to the use of LOAEL instead of NOAEL in the risk evaluation, the acceptable MOE is 300 or greater. The calculated MOEs for exposure intakes based on ingestion, migration or solubility modelling are shown in tables 4, 5 and 6, respectively.

Table 4: Calculated MOEs for the average and maximum exposure intakes due to mouthing of toys (ingestion method), using the LOAEL of 44 mg/kg bw/day established for kidney histopathology. MOEs below 300 are shown in bold font.

Age group (months)	LOAEL (mg/kg bw/day)	Ingestion intake (mg/kg bw/day)	MOE

0 - 3	44	-	-
3 - 6	44	0.207	**212**
6 - 9	44	0.177	**249**
9 - 12	44	0.161	**273**

Age group (years)	LOAEL (mg/kg bw/day)	Ingestion intake (mg/kg bw/day)	MOE
1-2	44	0.130	338
2-3	44	0.095	462
3-6	44	0.060	738

Table 5: Calculated MOEs for the average and maximum exposure intakes (mg/kg bw/day) due to mouthing of toys (migration method), using the LOAEL of 44 mg/kg bw/day established for kidney histopathology.

Age group (months)	LOAEL (mg/kg bw/day)	Migration average intake (mg/kg bw/day)	Migration maximal intake (mg/kg bw/day)	MOE (average intake)	MOE (maximum intake)
0 - 3	44	0.0002	0.001	220000	44000
3 - 6	44	0.014	0.077	3142	571
6 - 9	44	0.016	0.096	2750	458

9 - 12	44	0.009	0.025	4889	1760

Age group (years)	LOAEL (mg/kg bw/day)	Migration average intake (mg/kg bw/day)	Migration maximal intake (mg/kg bw/day)	MOE (average intake)	MOE (maximum intake)
1-2	44	0.005	0.020	8800	2200
2-3	44	0.003	0.029	14667	1517
3-6	44	0.001	0.009	44000	4889

Table 6: Calculated MOEs for the average and maximum exposure intakes due to mouthing of toys (solubility method), using the LOAEL of 44 mg/kg bw/day established for kidney histopathology. MOEs below 300 are shown in bold font.

Age group (months)	LOAEL (mg/kg bw/day)	Solubility average intake (mg/kg bw/day)	Solubility maximal intake (mg/kg bw/day)	MOE (average intake)	MOE (maximum intake)
0 - 3	44	0.0015	0.006	29333	7333
3 - 6	44	0.119	0.657	370	**67**
6 - 9	44	0.141	0.816	312	**54**
9 - 12	44	0.076	0.214	579	**206**

Age group (years)	LOAEL (mg/kg bw/day)	Solubility average intake	Solubility maximal intake (mg/kg bw/day)	MOE (average intake)	MOE (maximum intake)

		(mg/kg bw/day)			
1-2	44	0.040	0.170	1100	**259**
2-3	44	0.023	0.244	1913	**180**
3-6	44	0.006	0.076	7333	579

In general, the calculated MOEs are highly dependent on the exposure model used to estimate daily TCEP exposure from mouthing of toys. The solubility method yielded the lowest MOEs that were under 300 for the worst case (maximum) exposure scenario in children under 3 years old. However, the average exposure estimates for toddlers derived using this model were >20 (average intake) or >120 (maximum intake) times higher than estimated based on biomonitoring data (exposure intake from all sources and routes) using the reverse dosimetry method. The MOEs derived using reported migration of the TCEP into the sweat like solution yielded the highest MOEs which were over 300 for average and worst case scenario (maximum) exposure estimates at all ages. The ingestion model that is based on the assumption of a child ingesting 0.55 g of foam per day due to intensive mouthing and a release of TCEP from the ingested foam yielded to MOEs under 300 up to the age of 1 year.

Uncertainties in the risk assessment

Uncertainties in any risk characterisation process arise from inadequate information, assumptions made during the process and variability in experimental conditions. There is a high degree of uncertainty in characterising the risks of TCEP to children.

Exposure

To develop realistic exposure concentrations, TCEP levels in consumer products would need to be paired with experimental results on the availability of TCEP compound to migrate from these products and enter the body (TERA, 2015). However, this information is generally unavailable for the chemical. Additionally, all models used contain multiple assumptions due to lack of TCEP-specific information, such as migration rates to saliva or the information of TCEP concentrations in toys in Australia. Therefore, while the models are assumed sufficient to support that mouthing is a significant exposure route in young children, the actual exposure intakes are difficult to estimate.

The assumption that the children will ingest 0.55 g foam per day due to mouthing is likely to be an overestimate and, therefore; the estimated amount ingested per day is too high. This assumption is based on the estimated 50 g of ingested foam due to extensive mouthing for 90 days. If density of the foam is estimated to be 0.5 g/cm^3, the total volume of foam ingested would be 100 cm^3 (10 cm x 10 cm x 1 cm piece). The children's exposure is expected to be prevented by parent interventions. This conservative amount was used and is highly protective of children at all the age groups considered in this assessment. It was recently concluded by SCHER that “regarding the ingestion of toy materials by children, further research is required on the amounts of different toy materials ingested and the frequency with which toy material is ingested” (SCHER, 2016). Similarly, the intake estimates derived from solubility methods are considered highly conservative. The estimate is based on the assumption that the amount of TCEP available from the foam remains constant. Given the level of depletion of the chemical in foam at the assumed level, this would only be possible if the toy was replaced very frequently with a similar toy.

Mouthing of objects containing TCEP, such as changing table pads, infant sleep positioners, portable crib mattresses, and upholstered furniture may be additional source for TCEP in infants and toddlers (EU RAR, 2008; Danish EPA, 2014) but are not considered in this assessment. However, the assumptions used for estimation of exposure intake due to mouthing in this assessment are considered highly conservative overestimates, and therefore expected to cover the additional intake from other sources than toys.

Exposure via other potential sources and routes is based on the available information from other agencies and may not be representative of the Australian population. However, the exposure routes and sources in Australia are expected to be similar to other countries. These estimates will provide sufficient reference point to compare the extent of potential exposure intake via mouthing of toys to other exposure sources and routes.

Biomonitoring

Several uncertainties are associated with the estimation of daily intakes based on reverse dosimetry. The suitability of TCEP or its metabolites BCEP or DCEP for human biomonitoring is uncertain. Additionally, no information is available for the toxicokinetics of TCEP in humans or for different age groups and as such, estimates were based on experimental rodent studies. While urine concentrations based on TCEP levels measured in Australian toddlers were used in estimating the intake, other studies have measured BCEP or DCEP rather than TCEP levels in urine. Applying the generic mean urine volumes is also uncertain (Environment & Health Canada, 2016). Therefore, in order to derive reliable estimates using reverse dosimetry, further information would be required on the metabolism and excretion of TCEP in humans.

Hazard

The hazard profile in this assessment is based on the Tier II assessment of TCEP conducted by NICNAS. The assessment does not include full analysis of potential mechanisms of toxicity for TCEP or consider the potential differences between humans and experimental animals. In general, the kidney tumours are commonly observed following exposure to various chemicals in rodents (Lock & Hard, 2004). Additionally, data are lacking on the health effects of TCEP in young and/or adult humans following repeated exposure. The use of LOAEL instead of NOAEL is not preferred, given the uncertainty on the relevance of the TCEP-induced tumourigenesis to humans as well as the lack of understanding on the possible mode of action. This increases the uncertainty of the assessment of risk, although this is not as significant a concern given that the LOAEL is from a 2-year study rather than a 90-day study.

NICNAS Recommendation

The chemical TCEP exposure due to mouthing of polyurethane toys may be a significant exposure route for Australian children, especially under age of three. Based on experimental evidence, the critical health effects include carcinogenicity, reproductive toxicity and toxic effects of TCEP on liver, kidney and brain following long term oral exposure (as described in Tier II Human Health assessment of TCEP; NICNAS). Due to potential for exposure of children to TCEP via mouthing of toys and the critical health effects, it is concluded that the presence of TCEP in children’s toys can pose a risk for human health.

However, insufficient information exists to reliably estimate the risk for TCEP-induced health effects due to mouthing of toys. There are uncertainties in both the exposure and hazard assessments. The calculated MOEs are highly dependent on the exposure model used to estimate daily TCEP exposure from mouthing of toys and are considered to be overestimates as supported by the Australian biomonitoring data. As described under ***Uncertainties in the risk assessment***, there is evidence that the higher exposure estimates are very conservative and are not consistent with biomonitoring evidence. The use of TCEP is also expected to decline due to international regulations. Therefore, no further risk management is recommended at present.

Advice for consumers

Products containing the chemical should be used according to instructions on the label.

Advice for industry

The advice provided in the human health Tier II IMAP report remains unchanged, noting that from 1 January 2017, the chemical classification and labelling is aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and that under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

Abdallah MA, Covaci A, 2014. Organophosphate flame retardants in indoor dust from Egypt: implications for human exposure. Environ Sci Technol 48(9):4782-9. doi: 10.1021/es501078s.

Agency for Toxic Substances & Disease Registry (ATSDR) 2012. Phosphate Ester Flame Retardants. Accessed at http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1119&tid=239

Albertini R, Bird M, Doerrer N, Needham L, Robison S, Sheldon L, Zenick H, 2006. The use of biomonitoring data in exposure and human health risk assessments.

Environ Health Perspect 114(11):1755-62.

Albertini R, Bird M, Doerrer N, Needham L, Robison S, Sheldon L, Zenick H, 2006. The use of biomonitoring data in exposure and human health risk assessments. Environ Health Perspect 114(11):1755-62.

Brandsma SH, de Boer J, van Velzen MJ, Leonards PE, 2014. Organophosphorus flame retardants (PFRs) and plasticizers in house and car dust and the influence of electronic equipment. Chemosphere 116:3-9. doi:10.1016/j.chemosphere.2014.02.036.

Bretz WA, do Valle EV, Jacobson JJ, Marchi F, Mendes S, Nor JE, Cançado MF, Schneider LG, 2001. Unstimulated salivary flow rates of young children.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod 91(5):541-5.

Brommer S, Harrad S, 2015. Sources and human exposure implications of concentrations of organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices. Environ Int 83:202-7. doi: 10.1016/j.envint.2015.07.002.

Canada Gazette, 2014. Regulations Amending Schedule 2 to the Canada Consumer Product

Safety Act (TCEP). 146, 3114-3127. Available at http://www.gazette.gc.ca/rp-pr/p2/2014/2014-04-23/html/sor-dors79-eng.php

Canbaz D, van Velzen MJ, Hallner E, Zwinderman AH, Wickman M, Leonards PE, van Ree R, van Rijt LS, 2016. Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. Indoor Air. 26(3):403-13. doi: 10.1111/ina.12221.

Cao Z, Xu F, Covaci A, Wu M, Wang H, Yu G, Wang B, Deng S, Huang J, Wang X, 2014. Distribution patterns of brominated, chlorinated, and phosphorus flame retardants with particle size in indoor and outdoor dust and implications for human exposure. Environ Sci Technol 48(15):8839-46. doi: 10.1021/es501224b.

Cequier E, Ionas AC, Covaci A, Marcé RM, Becher G, Thomsen C, 2014. Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. Environ Sci Technol 48(12):6827-35. doi: 10.1021/es500516u.

United States (US) Consumer Product Safety Commission (CPSC), 2013. Toxicity Review of Tris(2-Chloroethyl) Phosphate (TCEP), Toxicology Excellence for Risk Assessment (TERA) And The Lifeline Group. Accessed at https://www.cpsc.gov/s3fs-

public/pdfs/TCEP-contract-report-with-cover-letter.pdf

Danish Environmental Protection Agency (Danish EPA), 2014. Survey, health and environmental assessment of flame retardants in textiles Survey of chemical substances in consumer products No. 126. Accessed at http://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-35-9.pdf

Danish Environmental Protection Agency (Danish EPA), 2015. Chemical substances in car safety seats and other textile products for children. Survey of chemical substances in consumer products No. 135. Accessed at http://www2.mst.dk/Udgiv/publications/2015/04/978-87-93352-07-0.pdf

Danish Environmental Protection Agency (Danish EPA), 2016. Chlorinated phosphorous-based flame retardants in children's articles containing foam. Background for content and possibilities for prevention in the EU. Environmental project No. 1855, 2016. Accessed at http://www2.mst.dk/Udgiv/publications/2016/05/978-87-93435-69-8.pdf

Dodson RE, Van den Eede N, Covaci A, Perovich LJ, Brody JG, Rudel RA, 2014.

Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environ Sci Technol 48(23):13625-33.

enHealth, 2012. Australian Exposure Factor Guide. The Department of Health. Environmental Health Publications. Accessed at http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-publicat-environ.htm

European Commission (EC) Directive 2009/48/EC. Appendix C of The Toy Safety Directive 2009/48/EC amendment in June 2014. Accessed at http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32014L0079

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2003. Technical Report No 86. Derivation of Assessment Factors for Human Health Risk Assessment.

European Union Risk Assessment Report (EU RAR), Tris(2-chloroethyl)phosphate, TCEP. CAS No 115-8-96-8. Accessed at https://echa.europa.eu/documents/10162/2663989d-1795-44a1-8f50-153a81133258

Environment & Health Canada, 2009. Final Screening Assessment for the Challenge. Ethanol,2-chloro-,phosphate (3:1) or tris(2-chloroethyl) phosphate (TCEP) (Cas No 1151-96-8). Accessed at http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot_5_e.html

Environment & Health Canada, 2016. Draft Screening Assessment of Certain Organic Flame Retardants Substance Grouping. 2-Propanol, 1chloro-, phosphate (3:1) (TCPP; CAS No 13674-84-5) and 2-Propanol, 1,3dichloro-, phosphate (3:1) (TDCPP; CAS No 13674-87-8). Accessed at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=B4374491-1

Fang M, Webster TF, Gooden D, Cooper EM, McClean MD, Carignan C, Makey C, Stapleton HM, 2013. Investigating a novel flame retardant known as V6: measurements in baby products, house dust, and car dust. Environ Sci Technol 47(9):4449-54. doi: 10.1021/es400032v.

Fromme H, Lahrz T, Kraft M, Fembacher L, Mach C, Dietrich S, Burkardt R, Volkel W, Goen T, 2014. Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). Environ Int 71:158-63. doi: 10.1016/j.envint.2014.06.016.

Harrad S, Brommer S, Mueller JF, 2016. Concentrations of organophosphate flame retardants in dust from cars, homes, and offices: An international comparison. Emerging Contaminants 2(2), 66–72.

He R, Li Y, Xiang P, Li C, Zhou C, Zhang S, Cui X, Ma LQ, 2016. Organophosphorus flame retardants and phthalate esters in indoor dust from different microenvironments: Bioaccessibility and risk assessment. Chemosphere 150:528-35. doi: 10.1016/j.chemosphere.2015.10.087.

He CT, Zheng J, Qiao L, Chen SJ, Yang JZ, Yuan JG, Yang ZY, Mai BX, 2015.

Occurrence of organophosphorus flame retardants in indoor dust in multiple microenvironments of southern China and implications for human exposure.

Chemosphere 133:47-52. doi: 10.1016/j.chemosphere.2015.03.043.

Hou R, Xu Y, Wang Z, 2016. Review of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research. Chemosphere 153:78-90. doi: 10.1016/j.chemosphere.2016.03.003. Review.

International Agency for Research on Cancer (IARC), 1997. Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis. Scientific Publications No. 147. Accessed December 2016 at https://monographs.iarc.fr/ENG/Publications/pub147/IARCpub147.pdf

International Agency for Research on Cancer (IARC), 1999. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. Volume 73. Accessed at http://monographs.iarc.fr/ENG/Monographs/vol73/mono73.pdf

Isaacs KK, Glen WG, Egeghy P, Goldsmith MR, Smith L, Vallero D, Brooks R, Grulke CM, Özkaynak H, 2014. SHEDS-HT: an integrated probabilistic exposure model for prioritizing exposures to chemicals with near-field and dietary sources.

Environ Sci Technol 48(21):12750-9. doi: 10.1021/es502513w.

Keimowitz AR, Strunsky N, Wovkulich K, 2016. Organophosphate flame retardants in household dust before and after introduction of new furniture. Chemosphere 148:467-72. doi: 10.1016/j.chemosphere.2016.01.048.

Keller AS, Raju NP, Webster TF, Stapleton HM, 2014. Flame Retardant Applications in Camping Tents and Potential Exposure. Environ Sci Technol Lett 1(2):152-155.

Kim JW, Isobe T, Muto M, Tue NM, Katsura K, Malarvannan G, Sudaryanto A, Chang KH, Prudente M, Viet PH, Takahashi S, Tanabe S, 2014. Organophosphorus flame retardants (PFRs) in human breast milk from several Asian countries.

Chemosphere 116:91-7. doi: 10.1016/j.chemosphere.2014.02.033.

Kim JW, Isobe T, Sudaryanto A, Malarvannan G, Chang KH, Muto M, Prudente M, Tanabe S, 2013. Organophosphorus flame retardants in house dust from the Philippines: occurrence and assessment of human exposure. Environ Sci Pollut Res Int 20(2):812-22. doi: 10.1007/s11356-012-1237-x.

Li P, Li Q-X, Ma Y-L, Jin J, Wang Y, Tian Y, Determination of Organophosphate Esters in Human Serum Using Gel Permeation Chromatograph and Solid Phase Extraction Coupled with Gas Chromatography-Mass Spectrometry. Chin J Anal Chem 43(7), 1033–1039.

Liu LY, He K, Hites RA, Salamova A, 2016. Hair and Nails as Noninvasive Biomarkers of Human Exposure to Brominated and Organophosphate Flame Retardants.Environ Sci Technol 50(6):3065-73. doi: 10.1021/acs.est.5b05073.

Lock EA, Hard GC, 2004. Chemically induced renal tubule tumors in the laboratory rat and mouse: review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. Crit Rev Toxicol 34(3):211-99.

Makinen MS, Mäkinen MR, Koistinen JT, Pasanen AL, Pasanen PO, Kalliokoski PJ, Korpi AM, 2009.Respiratory and dermal exposure to organophosphorus flame retardants and tetrabromobisphenol A at five work environments. Environ Sci Techno.43(3):941-7.

Malmgren-Hansen B, Olesen S, Pommer K, Funch LW, Pedersen E, Willum O, Olsen S, 2003. Emission and evaluation of chemical substances from selected electrical and

electronic products. Survey of Chemical Substances in Consumer Products, No. 32. Copenhagen (DK): Danish Ministry of Environment. Accessed at http://www.mst.dk/NR/rdonlyres/F6F58F52-2D13-48DC-B7B2-71A58387AC57/0/32.pdf

Matthews HB, Eustis SL, Haseman J, 1993. Toxicity and carcinogenicity of chronic

exposure to tris(2-chloroethyl)phosphate. Fundam Appl Toxicol 20: 477–485.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). IMAP Tier II Human Health Assessment for2-chloro-, phosphate (3:1). Accessed at www.nicnas.gov.au.

National Toxicology Program (NTP) 1991. Toxicology and carcinogenesis

studies of tris(2-chloroethyl)phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F1 mice (gavage studies). NTP Technical Report 391.

Petropoulou SS, Petreas M, Park JS, 2016. Analytical methodology using ion-pair liquid chromatography-tandem mass spectrometry for the determination of four di-ester metabolites of organophosphate flame retardants in California human urine.

J Chromatogr A 1434:70-80. doi: 10.1016/j.chroma.2016.01.020.

Poma G, Glynn A, Malarvannan G, Covaci A, Darnerud PO, 2017. Dietary intake of phosphorus flame retardants (PFRs) using Swedish food market basket estimations. Food and Chemical Toxicology 100, 1-7.

Safer States. Bill Tracker for Toxic Flame Retardants. Accessed at http://www.saferstates.org/toxic-chemicals/toxic-flame-retardants/

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed at http://hcis.safeworkaustralia.gov.au/

Schreder ED, Uding N, La Guardia MJ, 2016. Inhalation a significant exposure route for chlorinated organophosphate flame retardants. Chemosphere 150:499-504. doi: 10.1016/j.chemosphere.2015.11.084.

Scientific Committee on Health and Environmental Risks (SCHER), 2016. Final Opinion on

Estimates of the amount of toy materials ingested by children. Accessed at

http://ec.europa.eu/health//sites/health/files/scientific_committees/environmental_risks/docs/scher_o_170.pdf

Scientific Committee on Health and Environmental Risks (SCHER), 2012. Opinion on tris(2-chloroethyl)phosphate (TCEP) in Toys. Accessed at http://ec.europa.eu/health//sites/health/files/scientific_committees/environmental_risks/docs/scher_o_158.pdf

Stapleton HM, Sharma S, Getzinger G, Ferguson PL , Gabriel M, Webster TF, Blum A, 2012. Novel and High Volume Use Flame Retardants in US Couches Reflective of the 2005 PentaBDE Phase Out. Environ Sci Technol 46 (24), 13432-13439.

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF, 2009.

Detection of organophosphate flame retardants in furniture foam and U.S. house dust.

Environ Sci Technol43(19):7490-5.

Stapleton HM, Klosterhaus S, Keller A, Ferguson PL, van Bergen S, Cooper E, Webster TF, Blum A, 2011. Identification of flame retardants in polyurethane foam collected from baby products. Environ Sci Technol 45(12):5323-31. doi: 10.1021/es2007462.

Sundkvist AM1, Olofsson U, Haglund P, 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. J Environ Monit 12(4):943-51. doi: 10.1039/b921910b.

Swedish Environmental Protection Agency (Swedish EPA), 2016. Phosphorous flame retardants in Swedish market basket food samples, and estimation of per capita intake. Report to the Swedish EPA (the Health-Related Environmental Monitoring Program). Överenskommelse nr 2215-15-010. Accessed at https://www.diva-portal.org/smash/get/diva2:953241/FULLTEXT01.pdf

Tajima S, Araki A, Kawai T, Tsuboi T, Ait Bamai Y, Yoshioka E, Kanazawa A, Cong S, Kishi R, 2014. Detection and intake assessment of organophosphate flame retardants in house dust in Japanese dwellings. Sci Total Environ 478:190-9. doi: 10.1016/j.scitotenv.2013.12.121.

Toxicology Excellence for Risk Assessment (TERA), 2015. Environmental Concentrations and Consumer Exposure Data for Tris(2-Chloroethyl)Phosphate (TCEP). Accessed at https://www.cpsc.gov/s3fs-public/pdfs/CPSCStaffStatementToxicologyExcellenceRiskAssessmentsReportExposureDataTCEP.pdf

USGS. Presence and Distribution of Organic Wastewater Compounds in Wastewater, Surface, Ground, and Drinking Waters, Minnesota, 2000-02. Scientific Investigation Report 2004-5138. http://pubs.usgs.gov/sir/2004/5138/20045138.pdf

United States Environmental Protection Agency (US EPA), 2015a. TSCA Work Plan Chemical problem Formulation and Initial Assessment. Chlorinated Phosphate Ester Cluster Flame Retardants. Accessed at https://www.epa.gov/sites/production/files/2015-09/documents/cpe_fr_cluster_problem_formulation.pdf

United States Environmental Protection Agency (US EPA), 2015b. Flame Retardants used In Flexible Polyurethane Foam: An Alternatives Assessment Update. EPA 744-r-15-002. Accessed at https://www.epa.gov/sites/production/files/2015-08/documents/ffr_final.pdf

Van den Eede N, Maho W, Erratico C, Neels H, Covaci A, 2013. First insights in the metabolism of phosphate flame retardants and plasticizers using human liver fractions. Toxicol Lett. 223(1):9-15. doi: 10.1016/j.toxlet.2013.08.012

Van den Eede N, Heffernan AL, Aylward LL, Hobson P, Neels H, Mueller JF, Covaci A, 2015. Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environ Int. 2015 Jan;74:1-8. doi: 10.1016/j.envint.2014.09.005.

Washington State, 2014. Flame Retardants in General Consumer and Children's Products. Publication No. 14-04-021. Department of Ecology, State of Washington. Accessed at https://fortress.wa.gov/ecy/publications/documents/1404021.pdf

Wu M, Yu G, Cao Z, Wu D, Liu K, Deng S, Huang J, Wang B, Wang Y, 2016. Characterization and human exposure assessment of organophosphate flame retardants in indoor dust from several microenvironments of Beijing, China. Chemosphere 150:465-71. doi: 10.1016/j.chemosphere.2015.12.111.

Yang F, Ding J, Huang W, Xie W, Liu W, 2014. Particle size-specific distributions and preliminary exposure assessments of organophosphate flame retardants in office air particulate matter. Environ Sci Technol 48(1):63-70. doi: 10.1021/es403186z.

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