Scientific Committee on Health and Environmental Risks

SCHER

Opinion on tris(2-chloroethyl)phosphate (TCEP) in Toys

The SCHER adopted this opinion at its 16th plenary on 22 March 2012

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Opinions on risks related to pollutants in the environmental media and other biological and physical factors or changing physical conditions which may have a negative impact on health and the environment, for example in relation to air quality, waters, waste and soils, as well as on life cycle environmental assessment. It shall also address health and safety issues related to the toxicity and eco-toxicity of biocides.
It may also address questions relating to examination of the toxicity and eco-toxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment. In addition, the Committee will address questions relating to methodological aspect of the assessment of health and environmental risks of chemicals, including mixtures of chemicals, as necessary for providing sound and consistent advice in its own areas of competence as well as in order to contribute to the relevant issues in close cooperation with other European agencies.

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http://ec.europa.eu/health/scientific_committees/environmental_risks/members_wg/index_en.htm

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1. BACKGROUND

The substance tris(2-chloroethyl)phosphate (TCEP) is an alkyl phosphate ester used as a flame-retardant plasticiser and viscosity regulator in polyurethanes, polyester resins, polyacrylates and other polymers. The main industrial branches in which TCEP has been used are the building industry (e.g., roofing insulation, accounting for more than 80% uses in the EU), the furniture and the textile industry (e.g., back-coatings for carpets and upholstery). In addition uses are reported also in the manufacture of cars, railways and aircrafts, in professional paints, varnishes and lacquers (IPCS 1998; EURAR on TCEP 2009, Canadian Report on TCEP 2009).

However, production and use has been in decline since the 1980s, when TCEP has been progressively replaced by other flame retardants. TCEP was comprehensively evaluated under the EU existing substances regulation (EEC) 793/93 in 2009: the RAR reported that starting from 2001-2002 there is no production of TCEP in the EU, according to specific information given by industry.

TCEP has been identified in indoor and outdoor air, dust, drinking water, surface water and groundwater, as well as in various food products. It has also been detected in polyurethane foam that may be found in furniture and in toys.

2. TERMS OF REFERENCE

Recently SCHER gave their opinion (SCHER 2010) on the risks from organic CMR substances in toys, stating in particular that the presence of CMR category 2, when characterized by a threshold mechanism, can be accepted, pending a case-by-case evaluation. This evaluation should be based on available toxicological data (to derive a TDI) compared with exposure data, in order to identify possible risks.

With the present mandate, DG Enterprise would like to seek the advice of the Scientific Committee on the expected risks of CMRs in toys when their concentration limits are below those set up under the classification and labeling legislation. Please find enclosed, for the consideration by the Scientific Committee, two documents that provide concrete examples of concerns raised by the German authorities about the adequacy of the level of protection provided by the limits on CMR substances in the recently revised Toys Safety Directive 2009/48/EC.

DG Enterprise would therefore like an opinion on the following questions:

1) Is the Committee of the opinion that there are risks when TCEP (or its halogenated alternatives) is used in toys or part of the toys intended for use by children under 36 months or in other toys intended to be placed in the mouth in concentrations limit below those set up under the classification and labeling legislation and that lower concentration limits should be set for TCEP?

If yes, can the Scientific Committee suggest a specific limit value for TCEP taking into account the EU RAR and other available information? Can this limit value be based on the TDI of TCEP if it is known?

2) Is the Committee of the opinion that there are risks when TCEP (or its halogenated alternatives) is used in toys or part of the toys intended for use by children above 36 months in individual concentrations equal to or smaller than the relevant concentrations set up under the classification and labeling legislation?.

3. SCIENTIFIC RATIONALE

3.1. Sources of TCEP

TCEP is a non-volatile liquid at room temperature (vapour pressure = 114 $x10^{-5}$ Pa at 20°C); in normal conditions, inhalation exposure is mainly related to dusts containing TCEP formed primarily by abrasion. Indeed, TCEP has been measured in dust and particulate matter PM_{10} and $PM_{2.5}$ in indoor locations in Sweden and Germany in the range ≤10 to 2200 mg/kg (Hansen et al. 2001; Ingerowski et al. 2001; Marklund et al. 2003), with the highest concentration being found in schools (Hansen et al. 2001). It has been estimated that the 95th percentile of this distribution is 11.9 mg/kg, and the median 0.6 mg/kg.

TCEP was also measured in indoor air in homes, offices, schools, cars at values ranging from not detected up to 6000 ng/m^3, with the highest value found in a school in Germany. The 95th percentile as estimated in the EURAR on TCEP (2009) was 134 ng/m³ with a median of 10 ng/m³. The presence of TCEP has been primarily attributed to emissions from indoor sources (EURAR on TCEP 2009; Marklund et al. 2005; Ingerowski et al. 2001). In a study on chemicals found in electrical and electronic products, TCEP was detected in emissions from television sets at rates of <0.01–0.3 µg/h per set (n=10) (Malmgren-Hansen et al. 2003). Although physically present within the polymer matrix, TCEP can be emitted due to its migration to the surface and release from plastic products, giving rise to an additional potential source of exposure. This phenomenon is called "blooming," which refers to the diffusion of an ingredient in rubber or plastic material to the outer surface after curing. Trisphosphates in general are known to bloom from rigid plastics, although the degree of migration from the materials is not known.

Dermal exposure can occur from direct contact with e.g. furniture coverings, as well as with dust: no information is available on TCEP dermal exposure. The only available data is from the National Research Council (NRC, 2000), which has estimated dermal exposures of 0.003 mg/kg bw/d and 1.5 mg/kg bw/d for substances similar to TCEP, tris(1,3-dichloropropyl-2)phosphate (TDCP) and tris-monochloro-propyl phosphate (TCPP), respectively.

Oral exposure can occur due to dust intake, hand-to-mouth behaviour, and contamination of articles for daily use, e.g. toys which can be put into the mouth. Relevant for the oral route, TCEP was also found in drinking water, where concentrations ranged from not-detectable to 52 ng/L. (Canadian Report, 2009)

The Toy Industry of Europe (TIE) declared to the Commission that TCEP is no more used in toys manufacturing by the main producers in the EU, given its potential hazard. Nonetheless, as toys are heavily imported from non-EU countries its presence in toys on the EU market cannot be excluded. Exposure scenarios related to toys use may be of particular importance for children.

The use of TCEP in toys has been described in a draft report of the Danish Environmental Protection Agency of the Danish Ministry of Environment (Danish EPA, 2004, as referred to in the EU-RAR), containing information on concentrations of TCEP in toys and children's products. In baby products, TCEP was not detected above the detection limit of 1 mg/kg in any of the six products sampled (Tønning et al. 2008). Two different studies were conducted on toys. In 8 different toys produced from foam plastic, TCEP was not detected above the detection limit (50 mg/kg) (Borling et al. 2006). In another study, one out of the five toys sampled contained TCEP. It was a soft 10 x 10 x 10 cm cube made of textile, plastic and foam rubber, recommended for 0 months and above; the core of the cube consists of polyurethane (PUR) foam, accounting for half of the weight of the total cube (100 g).

Throughout the draft Danish report (2004) different values of TCEP content in PUR foam were reported (3300, 5200 and 6500 mg TCEP/kg), whereas the textile had a content of 160 mg TCEP/kg. Four products did not contain TCEP above the detection limit, which was not specified. The final version of the Danish EPA draft report (2006) reported only the average total TCEP content to be 5900 mg/kg, without giving any further detail. It is reported that the cube is no longer available in Denmark (Glensvig and Ports, 2006).

3.2. Toxicological profile of TCEP

After oral administration to rats, more than 90% of the TCEP dose is absorbed by the gastro-intestinal tract and systematically distributed with the higher concentrations found in liver, kidney, fat and the gastro-intestinal tract up to 24h after administration. An enterohepatic circulation is supposed to occur. Metabolism and elimination are the same after single and repeated application. Metabolites in urine were identical in rats and mice, although mice excreted more than 70% of a single oral dose of TCEP in an 8-hour period compared with 40% in rats (Matthews et al., 1990).

Absorption rates include the desorption of TCEP from dust and the subsequent absorption in the gastro-intestinal tract, the skin or in the lungs. No specific data are available on dermal and inhalation exposure of TCEP. Experimental data in rats and rabbits on the structurally related TDCP (tris[2-chloro-1-(chloromethyl)ethyl]phosphate) suggest it is absorbed extensively from the skin, although the rate and the exact extent were not measured (NRC, 2000). In the EU-RAR the absorption values were set to 100% for all the exposure routes as a 'worst case' approach.

Tris(2-chloroethyl)phosphate has moderate acute oral toxicity (oral LD_{50} for rats in the range of 430-1230 mg/kg bw) and is not classified for inhalation or dermal acute toxicity. TCEP is not an irritant for either skin or eyes. Based on information on structurally related chloroalkyl-phosphates TCPP (tris(2-chloro-methylethyl)phosphate) and TDCP, TCEP is not expected to be a human skin sensitizer (EU-RAR for TCEP, 2009).

Results of short- and long-term oral toxicity studies indicate that the brain, kidney and liver are the main target organs of toxicity in experimental animals. Similar effects were observed in rats and mice, although they occurred at higher doses in mice, likely due to differing rates of metabolism and elimination. Non-neoplastic effects were observed in the liver and kidneys of rats and mice in short-term and long-term repeated-dose studies; impaired fertility in mice and testicular toxicity in mice and rats were also described. The critical effects for risk characterization are linked to TCEP carcinogenicity, i.e., kidney tumours in rats and mice, thyroid tumours in rats and liver tumours in mice.

In long term oral toxicity studies kidney effects observed in rats and mice were dose- and time-related with respect to incidence and severity. In F344/N rats and B6C3F1 mice, a NOAEL for kidney lesions could not be estimated, since effects were observed in animals of both sexes at the lowest dose tested. The derived LOAELs were 44 mg/kg bw/d and 175 mg/kg bw/d in rats and mice respectively. The lowest LOAEL for kidney lesions (12 mg/kg bw/d) was identified in a chronic toxicity study with TCEP administered to Scl:ddY mice. The onset of kidney lesions can be considered as the critical effect, and the lowest LOAEL of 12 mg/kg bw/d chosen as the basis for risk characterisation.

Results from short and long term studies suggested some potential neurotoxicity for TCEP. Neuronal effects in the hippocampus and cell loss in the brain of rats were observed in a 16 week-toxicity study by gavage (NOAEL 88 mg/kg bw/d); the NOAEL for male and female mice for convulsion and ataxia was 175 mg/kg bw/d. When serum cholinesterase activity was tested inhibition was measured in female F344/N rats at 175 and 350 mg/kg bw/d TCEP, but not in male rats. The effect was not observed in B6C3F1 mice of both sexes in subacute/subchronic studies up to 700 mg/kg bw/d. Therefore, the inhibition of serum cholinesterase activity cannot be considered as a critical early end-point to predict any adverse effect.

The only data available on humans is related to a case report about neurotoxic signs progressing to paresis, experienced by a 5 year old child (Ingerowski & Ingerowski, 1997). Exposure to TCEP was postulated since the child slept in a room in which wood panelling treated with wood preserver containing 3% TCEP were present (600 mg/kg of wood). TCEP was not determined in house dust, and therefore exposure could not be quantified. However, symptoms increased with increasing time of exposure and ceased after discontinuation, indicating a possible relationship between TCEP exposure and the neurotoxic signs.

In addition, an epidemiological study carried out in Austria is available, aimed to investigate the effects of a number of airborne pollutants (including particulates and TCEP) in the school environment on the respiratory health of children (5-9 years of age) and on some cognitive abilities. The report postulated an association between the TCEP content of airborne dusts and children's cognitive abilities (UBA, 2008), although not all potential confounding factors were adjusted for in the statistical analyses, strongly limiting the data interpretation.

TCEP was not mutagenic in most in vitro bacterial mutation assays and with mammalian cells. Very weak effects were obtained in in vitro SCE tests. Negative or equivocal results were also obtained in in vivo micronucleus assay, following application up to maximum tolerated doses. TCEP did not induce somatic cell chromosomal damage in an in vivo assay in Drosophila melanogaster. On this basis it can be concluded that TCEP shows no relevant potential for genotoxicity.

Carcinogenicity studies provide clear evidence that TCEP is carcinogenic in rats and mice at various organ sites. In 2-year studies in rats and mice dosed orally with TCEP, increased incidences of renal tubule adenomas (both sexes of rats, male mice), renal tubule carcinomas (male mice) were observed. In rats, the renal tubule tumours showed a dose-related increase at 44 mg/kg bw/d and statistically significantly high incidences at 88 mg/kg bw/d. In mice, these tumours showed increases in incidence at doses of 300 and 1500 mg/kg bw/d, whereas a markedly increased incidence of Harderian gland adenomas was reported at the lowest tested dose of 175 mg/kg bw/d (Takada et al. 1989; NTP 1991; Matthews et al. 1993).
In addition, increased incidences of thyroid follicular adenomas or carcinomas (female rats), leukaemia (female mice), hepatocellular adenoma and carcinoma (male mice), forestomach papilloma and squamous cell carcinoma (female mice), Harderian gland adenomas and carcinomas (female mice) were observed.

TCEP was carcinogenic following oral administration also in male Scl:ddY mice, with a dose-related increased incidence of tumours in the kidneys starting at 300 mg/kg bw/d and in the liver starting at 60 mg/kg bw/d (statistically significantly high incidences of tumours at 300 mg/kg bw/d). At the lowest dose tested (i.e. 12 mg/kg bw/d) increased rates of renal proliferative lesions and of cell atypia in renal tubule epithelium were observed and therefore a NOAEL for kidney effects could not be established. The NOAEL for liver tumour formation in this study is considered to be 60 mg/kg bw/d.

Based on results from the genotoxicity studies, the TCEP-induced tumours in rats and mice cannot be directly related to primary genotoxic effects and the occurrence of non genotoxic mechanisms can be expected. At least in the liver and in the kidneys, a non-genotoxic mechanism is made plausible by the observations of related non-neoplastic effects in short- and long-term studies with TCEP. Indeed, tumour formation can be considered secondary to cytotoxicity followed by cell proliferation mechanism, associated to the high rate of blood flow through both organ and their high metabolic capability. However, although it was recognized that there is no species-specificity in the mode of action, the mechanism of tumour development in TCEP treated rodent has not been elucidated so far. Also admitting the presence of a non-genotoxic mechanism, for renal

tumour formation a NOAEL could not be established and therefore no threshold dose was identified, whereas a dose level of 60 mg/kg bw/d is considered to be the NOAEL for tumour formation in the liver.

No data are available for thyroid tumours observed in rats or leukaemia observed in mice; the SCHER support the conclusion of the Canadian report on TCEP (2009) reporting that *'it cannot be precluded that TCEP induces tumours via a mode of action involving direct interaction with genetic material.'*

Overall, no conclusion can be drawn about the relevance of the TCEP-induced tumours to humans due to the lack of knowledge of the possible mode of action, but considering all available data, the relevance to humans of renal and hepatic tumours cannot be excluded. On this basis, TCEP has been classified as carcinogenic cat 2, R40.

TCEP shows reproductive toxicity in rodents, with significant impairment of reproductive success of both sexes. The evaluation of reproductive organs and sperm parameters in subchronic studies, allow to derive a LOAEL equal to 700 mg/kg bw/d in the mouse related to testicular toxicity. Testicular toxicity was also observed in male mice exposed to TCEP by inhalation at concentrations of 0.5 and 1.5 mg/m^3 for 4 months. When exposed males were mated with unexposed females, pre- and post-implantation loss was increased and litter size was decreased at 1.5 mg/m^3. Significant reduction of the number of litters produced by the F0 generation, reduced litter size in both the F0 and the F1 generations and reduced pregnancy and fertility indices in the F1 generation were observed in a 2-generation study in CD-1 mice with a NOAEL for fertility of 175 mg/kg bw/d.

TCEP shows no potential for embryo-/fetotoxicity or teratogenicity in rodents even at maternally toxic doses. A NOAEL for developmental toxicity of 200 mg/kg bw/d was derived, with a NOAEL for maternal toxicity of 100 mg/kg bw/d.
On the basis of its effects on fertility, TCEP is classified and labelled as reproductive toxicant cat 1B, H360F.

On the basis of these results renal lesions are confirmed as the critical toxicological end-point, since the derived LOAEL is lower than the NOAEL values identified for reproductive and developmental toxicity.

3.3. Exposure to TCEP

The exposure evaluation here is limited to children, being the opinion related to TCEP in toys. All the possible TCEP sources have been considered, for an adequate risk assessment.

<u>Oral.</u>
Oral exposure can be referred to dust intake, due to hand-to-mouth behaviour, contamination of articles for daily use, e.g. toys which can be put into the mouth.

For the TCEP uptake from house dust, the 95th and 99th percentile and the maximum for children, representing a vulnerable population due to their specific hand-mouth-behaviour are 0.1, 0.2, and 0.7 µg/kg bw/d, respectively. This estimate has been obtained by using a probabilistic approach based on the available experimental data; the calculations have been performed taking the @RISK-4.5-professional software tool (EU-RAR, 2009), considering 20 and 100 mg/d as normal and upper limit of dust intake by children.

The exposure from drinking water was calculated, starting from a content of 52 ng/L, a consumption of 1-1.5 L/d and an average bodyweight of 7.5 kg, to be in the range of 0.007-0.01 µg/kg bw/d.

It is not possible to give an adequate estimate of the TCEP exposure of children sucking on toys containing TCEP, due to the scant representativeness and reliability of the available data. Indeed, the Danish EPA report refers only to a single toy (soft cube made of textile, plastic and foam rubber), out of 5 sampled, which is not representative of the actual situation.

In addition, the method used for TCEP migration from the toy suffers some limitations and results were poorly reported.

Artificial, sweat-like solution (NaCl, ammonia, lactic acid, urea, and water as described in DS/EN 1811) was used instead of artificial saliva. A sample of approximately 5 grams consisting of partial amounts of all toy components was added with 100 ml artificial sweat and incubated at 40°C for 24 hours (longer than more realistic times for sucking activities). It can be noted that by cutting the TCEP containing foam, the surface exposed to the artificial sweat solution is larger, possibly leading to on overestimated migration. Following incubation, the artificial sweat was extracted with dichloromethane and an aliquot analysed with gas chromatography-mass spectrometry (GC/MS). TCEP total content in sweat was indicated as high as 3000 ppm (300 mg TCEP in 100 mL of the solution). Due to the lack of information on the method used and its limit of detection, the reliability of data on the amount of migrated TCEP cannot be adequately checked.

The calculation made for risk assessment by the Danish EPA and reported in the EU-RAR, assuming a 50% migration as a worst case scenario (see below), is not fully supported by the data and affected by a high degree of uncertainty. Indeed, if 300 mg TCEP were detected in 100 ml artificial sweat migrated from 5 g of the toy, the total TCEP content in the soft cube (100 g) should be almost equal to the total TCEP content, indicating 100% migration.

This is consistent with the consideration that, based on the TCEP water solubility (7.8g/L at 20°C; logPow= 1.78) (ECB, 2000; EU-RAR,2009) and blooming effect (i.e. very fast migration of TCEP from interior to outer surface), it can be qualitatively expected that the total TCEP content migrates from toys consisting of PUR foam or covered by textiles containing TCEP into aqueous media simulating saliva or sweat.

Keeping in mind the uncertainties described above, the calculation of TCEP exposure done by Danish EPA and endorsed by the EU-RAR, is based on the assumption that a 3 month-old baby plays with a cube for 3 months, during which the cube is sucked intensively. About 50% of the total amount of the TCEP is anticipated to be swallowed by the baby. Considering an average weight of 6 kg during the three months and a total TCEP content of 260 mg (50 g PUR foam with a content of 5200 mg TCEP/kg- the intermediate value among those indicated in the Danish Report) **a daily dose of 0.24 mg TCEP/kg bw/d can be calculated** [0.5 (total release factor) x 260 mg TCEP /(90 d x 6 kg)]. The Danish Report considers that the TCEP from the foam can also migrate through the textile layer during sucking, but this migration is not considered relevant, compared to the 8 mg TCEP content measured in the textile. As a whole, a daily dose of 7.4 µg TCEP/ kg bw/d was calculated.

The starting point of the Danish estimate is TCEP content from a single item. However, when the limit identified by the Toy Safety Directive (TSD) for reproductive toxicant cat 1B (0.5%) corresponding to a maximum amount of 5000 mg/kg toy is considered together with 100% migration of the TCEP content, results of exposure similar to the Danish estimate are obtained. However, it should be noted that this content could not be representative of the actual situations of toys on the market, most of which coming from

non-EU countries. Given that there is evidence that the amount of time spent mouthing peaks at 6-9 months of age (DTI, 2002), it is considered appropriate to assume that babies are exposed during the first year of age, with an average body weight of 7.5 kg (RIVM, 2008). In addition, having no information on the rate of migration, data obtained after 24h give no indication about the potential exposure during one hour sucking, which is considered a reasonable time for children aged up to 3 months, whereas those in the 6 to 9 month age range may mouth/suck toys for nearly 4 hours a day (DTI, 2002). Given a very rapid migration, the peak of TCEP swallowed would be higher during a shorter period of time than the per day amount.

In addition to the Danish EPA estimate, Health Canada (2009) also calculated the potential exposure due to a similar scenario. Exposure estimates for infants (0–6 months old) and toddlers (6 months to 4 years old) mouthing foam containing TCEP at a concentration equivalent to TCEP's water solubility were derived: 40 µg/kg bw/d for infants and 20 µg/kg bw/d for toddlers. The Canadian calculation is based on the application of methodology developed for another flame retardant by the US Environmental Protection Agency's Voluntary Children's Chemical Evaluation Program (Environ 2003a, b). Default values for ingestion from mouthing and TCEP values used by Health Canada were: water solubility (WS) of TCEP is 7820 mg/L, salivary flow rate in child's mouth (V_s) is 0.22 ml/min, convert L to mL (CF), fractional rate of extraction by saliva (FR) is 0.038, absorption factor by the oral route (AF_o) is 0.5, exposure frequency mouthing behaviour (EF_{mouth}) is 9 min/day (Environ 2003a, b), and body weight (BW) is 7.5 kg for infants and 15.5 for toddlers (Health Canada 1998).

Dose = (7820 mg/L × 0.22 ml/min × 0.001 L/ml × 0.038 × 0.5 × 9 min/day) / 7.5 kg or 15.5 kg

Inhalation.

The evaluation of TCEP uptake by inhalation was carried out in EU-RAR (2009) taking the same approach as described above for dust uptake. TCEP exposure through dust uptake by inhalation revealed a 95th, 99th percentile and a maximum value of 0.07, 0.96, and 3.9 µg/kg bw/d TCEP for a 3 year old child, for which a consumption of 100 mg dust per day (including soil) has been estimated.

Direct inhalation of TCEP was estimated to account for 0.96 µg/kg bw/d for children (99th percentiles), when considering 100% absorption and the data by Ingerowski et al. (2001), according to which the 98th percentile for air concentrations of TCEP is 0.6 µg/m³ (located at the extreme upper range of available measurements).

Dermal.

Dermal exposure can occur from direct contact with e.g. furniture coverings and toys, as well as with house dust and airborne dust. According to Bruckert and Schoene (1990) an amount of ≈130 µg/25cm² per 24 hours (= 0.217 µg/cm^2/h) of TCEP can be released from upholstery containing an amount of 8 mg/cm².

The dermal exposure for 1-3 year old children would account for 12.1 µg/kg bw/d (average body weight 7.5 kg), making the following assumption (similarly to what has been done in the EU RAR, 2009): 380 cm² as the area of contact with furniture covered by textiles (i.e. armchair, carpet) and 4 hour as contact time, leading to 329 µg/event (=0.217 µg/cm²/h * 4 h *380 cm²); 100 event per year and 7.5 kg as average body weight.

The dermal exposure to airborne dust can be neglected due to the very low concentration (below the nanogram-range) in contact with skin, whereas dermal exposure by house dust contact can be relevant for children. On the basis of experimental data in the EU-RAR a maximum load of ~5.0 mg of dust per hand in 1-4 year old children has been estimated (EU-RAR, 2009). Taking the 98th percentile of TCEP dust concentration reported by Ingerowski et al. (2001) (i.e. 18 ng/mg of house dust), than the total dermal

exposure via this pathway would account for ~0.18 µg per day (both hands), corresponding to 0.024 µg/kg bw/d (average body weight 7.5 kg)

When all the exposure paths (except the one due to mouthing/sucking toys containing TCEP) a total exposure for 1-3 year-old children is estimated around 13 µg/kg bw/d (Table 1)

Table 1: Calculation of TCEP daily exposure (µg/kg) of 1-3 year old children from different routes of exposure

Routes of TCEP exposure	Exposure (µg/kg bw/d)	Provisional TDI (µg/kg bw/d)
Dermal contact (textiles, furniture, dust)	12.12	
House dust, typical exp. (including soil)	0.1-0.7	
Direct inhalation	0.96	
Drinking water	0.01	
Total exposure	**13.19-13.79**	**13**
Migration into saliva	?* 240** 20 – 40***	

* According to SCHER, the database is not appropriate to derive a reliable estimate.
** Estimated intake as calculated on the basis of the Danish EPA Report
***Estimated intake as calculated by Health Canada for toddlers (6 months-4 years old) and infants (0-6 months old).

3.4. Risk characterization

Although TCEP is classified as carcinogen cat 2, a clear threshold for tumour induction cannot be identified and therefore the definition of a TDI could not be the ideal approach. Following the recommendation of SCHER/SCCP/SCENHIR opinion on risk assessment procedure to be followed for carcinogens (2009), the Margin of Exposure approach should be used. However, in the absence of a clearly defined BMD_{05}, a provisional TDI can be derived, by using the LOAEL for kidney effects after repeated exposure of 12 mg/kg bw/d as the point of departure. The Assessment Factors to be considered in a conservative approach should include the defaults for intra- and interspecies variability (10x10) and a factor of 3 accounting for the use of a LOAEL (in some cases depending on the quality of the data base, factor as high as 10 is used to address this point); an additional factor of 3 considering the uncertainties regarding the relevance of the TCEP-induced tumours to humans due to the lack of knowledge of the possible mode of action and the threshold for tumour induction has also been introduced. The calculated 'provisional' TDI is therefore 13 µg/kg bw/d. The daily burden coming from all the possible source of TCEP, excluding the toy scenario, corresponds to the same value. Although both values are obtained by using a conservative approach, considering that the TCEP from toys would add to the exposure coming from the other sources, it should be avoided in order to not exceed the reference value.

In light of the uncertainties in the databases on exposure and effects, including the fact that increased incidences of tumours were also observed at the critical effect level for non-cancer effects, it is considered that the estimated margins of exposure may not be adequately protective of human health.

3.5. TCEP halogenated alternatives

Due to human health concern, TCEP has been replaced with TCPP and TCDP, mostly in the manufacturing of PUR foam. Most of the TCPP and TDCP produced in the EU in 2000 were indeed used in the production of flexible and/or rigid PUR foam in the automotive industry, constructions and furniture. The foam is generally enclosed within an article, and in the EURAR of both compounds (2008) it is considered that consumers are not expected to come into direct contact with foams. However, in line with the TCEP risk assessment, TCPP and TCDP can be ingested with house dust following emission in indoor air. There is no specific information related to the use of TCPP and TCDP in toys: although based on the declaration of TIE to the Commission a significant use can be excluded in EU. However, this consideration does not apply to toys imported from non-EU countries.

In the following the toxicological profile of TCPP and TCDP will be briefly presented, mainly based on the data reported in the corresponding EU Risk Assessment Reports (EU-RAR on TCPP 2008, EU-RAR on TDCP 2008)

TCPP consists of four isomers, with a variable relative ratio in the commercial products, although their physical-chemical properties and toxicological characteristics are similar.
Based on experimental data, oral absorption is around 80%, whereas for the dermal absorption values of 23% and 40% has been reported for exposure to "neat" TCPP or due to handling of foam containing TCPP. For the inhalation route, 100% absorption is assumed.

TCPP is of low acute toxicity via the inhalation and dermal route and of moderate oral acute toxicity, with a NOAEL of 200 mg/kg bw/d. No acute delayed neurotoxicity was evidenced. TCPP is non-irritant in the rabbit eye and skin and has no skin sensitisation potential.

After TCPP administration in the diet for 13 weeks (the study of longest duration), the liver and thyroid were the main target organs. A LOAEL=52 mg/kg bw/d is derived, based on the increase in liver weights and mild thyroid follicular cell hyperplasia observed in males of all dose groups.

In a 2-generation reproductive toxicity study rats were fed TCPP in the diet for parental toxicity, a NOAEL =85 mg/kg bw/d was derived for males, whereas the LOAEL in females was 99 mg/kg bw/d, similar to the LOAEL of 99 mg/kg bw/d derived for developmental toxicity: the effects could not be considered independently on dam toxicity.

Overall, it is considered that TCPP is not genotoxic *in vitro* and *in vivo*. There are no carcinogenicity data for TCPP, which is structurally similar to TDCP and TCEP, which are both considered to be non-genotoxic carcinogens (Carc. cat 2, H351). The EU-RAR concluded that there is sufficient information from the structures, physical-chemical properties, toxicokinetics and mutagenic profiles of TCEP, TDCP and TCPP to support a qualitative read-across, indicating a potential concern for carcinogenicity for TCPP by a non-genotoxic mechanism. Due to lack of information on the mode of action for TCEP and TDCP, no quantitative read-across can be performed giving any prediction on a relatively potency of TCPP.

If subchronic effects were to progress to cancer via a non-genotoxic mechanism, the LOAEL of 52 mg/kg bw/d can be used as a basis for risk characterisation. By using the same approach as described for TCEP, the calculated 'provisional' TDI is therefore in the range 57-170 µg/kg bw/d .

TDCP was well absorbed by the oral route of exposure and based on available studies, 100% absorption will be assumed (as well as after inhalation). For the dermal absorption

values of 15% and 30% has been reported for exposure to "neat" TDCP or due to handling of foam containing TDCP. TDCP is rapidly and extensively (100%) metabolised, and excreted via the urine (approx 50%), faeces and expired air: no accumulation in the body is expected.

TDCP is of low acute toxicity following inhalation, oral and dermal routes of exposure. There is no evidence of TDCP induced delayed neurotoxicity. TDCP is non-irritant in the rabbit eye and skin and has no skin sensitisation potential.

In relation to repeated toxicity, a 2-year carcinogenicity study allowed the derivation of a LOAEL of 5 mg/kg bw/d, based on the hyperplasia of the convoluted tubule epithelium in the kidneys, considered a pre-neoplastic lesion, and testicular effects observed at this dose. In the same study significant increase in the incidence of renal cortical adenomas and an increased incidence of Leydig cell tumours in mid and high dose animals were observed. The mechanism by which TDCP induces such tumours is not known.

Although some evidence could suggest that TDCP is mutagenic *in vitro*, *in vivo* assays were all negative. This indicates that TDCP may be assumed to be a threshold carcinogen. Indeed, TDCP is classified as Carc. cat 2 H351.

An overall NOAEL of 100 mg/kg/day can be derived for developmental toxicity. By using the same approach as described for TCEP, the calculated 'provisional' TDI is therefore in the range 5-16 µg/kg bw/d .

4. OPINION

1) Is the Committee of the opinion that there are risks when TCEP (or its halogenated alternatives) is used in toys or part of the toys intended for use by children under 36 months or in other toys intended to be placed in the mouth in concentrations limit <u>below</u> those set up under the classification and labeling legislation and that lower concentration limits should be set for TCEP?

TCEP is very soluble in water and easily released from toys following children sucking and chewing activities. The absence of a reliable migration test did not allow quantitative assessment of the amount leached during mouthing in children, which, on the basis of its properties, can be expected to be substantial with respect to its total content in toys. In addition, exposure can occur by inhalation, mainly through dusts containing TCEP, formed primarily by abrasion and by the dermal route.

The Toy Industry of Europe (TIE) declared to the Commission that neither TCEP nor any of its halogenated structurally related substitutes are used any more in toys manufacturing by the main producers in EU. Based on its properties, TCEP is not retained within the article after sucking, losing its action as flame retardant.

According to the new Toy Safety Directive, TCEP which is classified as carcinogen category 2 (H351) and toxic to reproduction category 1B (H360F), may occur in toys up to a concentration of 0.5% (0.3% starting from 2015).

It is the SCHER opinion that the presence of CMR category 2 (according to the CLP regulation), can be accepted when characterized by a threshold mechanism, pending a case-by-case evaluation (SCHER opinion on CMR in toys, 2010). The evaluation should be based on available toxicological data, compared with exposure levels in order to identify possible risks. Considering the case of TCEP, it should be underlined that its

mode of action has not been identified for the multisite tumour formation, and it has not been possible to derive a clear threshold, since a LOAEL was derived.

However, a 'provisional' TDI of 13 µg/kg bw/d could be calculated. The daily burden coming from all the possible sources of TCEP, excluding the toy scenario, is similar to the TDI value. Considering that TCEP from toys would add to the exposure coming from the other sources, it should be avoided in order not to exceed the 'provisional' TDI. The SCHER concluded that no additional exposure from toys can be considered safe.

Taking into account data from the Danish EPA report, although with the uncertainties described above, the TCEP content in the soft cube toy was 0.5-0.6%, which is equal-to-higher than the limit indicated in the TSD (0.5% which will be 0.3% starting from 2015). The content would correspond to a risk for children using these toys, even without considering the other exposures.

There are no data about the use of TCEP halogenated alternatives in toys, or on their eventual content and/or migration in saliva due to mouthing habits in children. However, the SCHER agrees with the conclusion in the EURAR that there is sufficient information from the structures, physical-chemical properties, toxicokinetics and mutagenic profiles of TCEP, TDCP and TCPP to support a read-across. This would imply that considerations given for TCEP could be applied to its halogenated alternatives as well, if used in toy manufacturing.

1a) If yes, can the Scientific Committee suggest a specific limit value for TCEP taking into account the EU RAR and other available information? Can this limit value be based on the TDI of TCEP if it is known?

There is no reason to set any limit for TCEP in toys, since no safe limit could be identified based on the exposure from other sources. The limit should be set at the detection limit of a sufficiently sensitive analytical test method.

2) Is the Committee of the opinion that there are risks when TCEP (or its halogenated alternatives) is used in toys or part of the toys intended for use by children above 36 months in individual concentrations equal to or smaller than the relevant concentrations set up under the classification and labeling legislation?

Since the mouthing habits of children above 36 months is lower, it could be argued that the risk of exposure via the oral route linked to mouthing/sucking/chewing toys is lower. Nonetheless, it cannot be excluded. In addition, toys represent only one of the sources of TCEP exposure in indoor environment.

The daily burden for an adult from all the TCEP exposure paths as estimated in the EURAR was around 4.5 µg/kg bw/d, that is ≈50% of the one derived for 1-3 year-old children.

SCHER concludes that it can be expected that the exposure for children above 36 months lies in between the exposure estimates for adults and that for children below 3 years. Since the estimated exposure from all possible sources of TCEP, excluding the toy scenario, is close to the provisional TDI value, the use of TCEP should be avoided also in toys intended for use by children older than 3 years of age.

5. ABBREVIATIONS

Cat	category
bw	bodyweight
d	day
CMR	carcinogenic, mutagenic, and reprotoxic
CLP	Classification, labelling and packiging
EU-RAR	European Union Risk Assessment Report
NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level
IPCS	International Programme on Chemical Safety
TCEP	tris(2-chloroethyl)phosphate
TCPP	tris-monochloro-propyl phosphate
TDCP	tris(1,3-dichloropropyl-2)phosphate
TDI	Tolerable daily intake
TIE	Toy Industry of Europe
TSD	Toy Safety Directive
WHO	World Health Organization

6. REFERENCES

Borling P, Engelund B, Sørensen H, Cohr K.-H. 2006. Survey, migration and health evaluation of chemical substances in toys and childcare products produced from foam plastic. Survey of Chemical Substances in Consumer Products, No. 70 [Internet]. Copenhagen (DK): Danish Ministry of Environment. [cited 2008 Nov]. Available from: http://www2.mst.dk/udgiv/Publications/2006/87-7052-098-4/pdf/87-7052-099-2.pdf

Bruckert HJ and Schoene K (1990). Austritt von TRIS(2-Chlorethyl)Phosphat aus Bezugsstoffen für Sitzpolster. Fraunhofer Institut für Umwelthygiene und Ökotoxikologie; unpublished.

Canadian Report on TCEP, 2009. Ethanol, 2-chloro-, phosphate (3:1) (Tris(2-chloroethyl) phosphate [TCEP]) http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/summary-sommaire/batch-lot-5/115-96-8-eng.php,

Danish EPA, 2006 Survey and risk assessment of perfume and flavours in toys and childcare products. Survey of chemical substances in consumer products No. 68 2006 Mapping of perfume in toys and children's articles, http://www2.mst.dk/udgiv/publications/2006/87-7052-018-6/pdf/87-7052-019-4.pdf

DTI, 2002 Research into the mouthing behaviour of children up to 5 years old. Consumer and Competition Policy Directorate22010 DTI Mouthing rep cover 28/8/02 www.berr.gov.uk/files/file21800.pdf

Environ 2003a, b - US Environmental Protection Agency's Voluntary Children's Chemical Evaluation Program

EURAR on TCEP 2009, European Union Risk Assessment Report on Tris(2-chloroethyl) phosphate, (TCEP) http://www.baua.de/de/Chemikaliengesetz-Biozidverfahren/Dokumente/RAR-068.pdf?__blob=publicationFile&v=1

EURAR on TCPP 2008, European Union Risk Assessment Report on Tris(2-chloro-1-methylethyl) phosphate (TCPP)

EURAR on TDCP 2008, European Union Risk Assessment Report on Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP)

Glensvig D, Ports J. 2006. Mapping of perfume in toys and children's articles. Survey of Chemical Substances in Consumer Products, No. 68. Copenhagen (DK): Danish Ministry of Environment. [cited 2008 Nov]. Available from: http://www2.mst.dk/udgiv/Publications/2006/87-7052-018-6/pdf/87-7052-019-4.pdf

Hansen D, Volland G, Krause G, Zöltzer D. 2001. Determination and occurrence of phosphororganic compounds (POV) in dust and indoor air. Gefahrst Reinhalt der Luft 61(1–2): 13–17.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

IPCS 1998, International Programme on Chemical Safety, Internal Technical Report, Environmental Health Criteria for Tris (chloropropyl) phosphates, 1998

Ingerowski, R. and Ingerowski, G. 1997. Moegliche neurotoxische Wirkung des chlorierten Posphorsaeureesters Tris(2-chlor-ethyl)-phosphat-eine umweltmedizinishe Kazuiseik. Internist. Prax. 37, 229-230.

Ingerowski G, Friedle A and Thumulla J (2001). Chlorinated ethyl and isopropyl phosphoric acid triesters in the indoor environment - An inter-laboratory study. Indoor Air, 11, 145 - 149.

Marklund et al. 2003. Screening of organophosphorous compounds and their distribution in various indoor environments. Chemosphere 53, 1137-1146.

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 [Internet]. Copenhagen (DK): Danish Ministry of Environment. [cited 2008 Nov]. Available from: http://www.mst.dk/NR/rdonlyres/F6F58F52-2D13-48DC-B7B2-71A58387AC57/0/32.pdf

Matthews HB, Dixon D, Herr DW and Tilson H (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicol. Industr. Health, 6, 1-15.

Matthews HB, Eustis SL, Haseman J. 1993. Toxicity and carcinogenicity of chronic exposure to tris(2-chloroethyl)phosphate. Fundam Appl Toxicol 20: 477–485.

NRC 2000. National Research Council (US) 2000. Toxicological risks of selected flame-retardant chemicals. Washington (DC): The National Academy Press. http://www.nap.edu/openbook.php?record_id=9841&page=R2

NTP 1991. National Toxicology Program (US) 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. Research Triangle Park (NC): US Department of Health and Human Services, National Toxicology Program.

SCHER opinion on risk from organic CMR substances in toys, 18 May 2010, http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_121.pdf

RIVM (2008) Chemicals in Toys, RIVM report 320003001/2008

Takada K, Yasuhara K, Nakaji Y, Yoshimoto H, Momma J and Kurokowa Y (1989). Carcinogenicity study of tris(2-chloroethyl)phosphate in ddY mice. J. Toxicol. Pathol., 2, 213-222.

Tønning K, Pedersen E, Lomholt AD, Malmgren-Hansen B, Woin P, Møller L, Bernth N. 2008. Survey, emission and health assessment of chemical substances in baby products. Survey of Chemical Substances in Consumer Products, No. 90 [Internet]. Copenhagen (DK): Danish Ministry of Environment. [cited 2008 Nov]. Available from: http://www2.mst.dk/udgiv/publications/2008/978-87-7052-717-0/pdf/978-87-7052-718-7.pdf

UBA 2008 GUIDELINES FOR INDOOR AIR HYGIENE IN SCHOOL BUILDINGS. Produced by the German Federal Environment Agency's Indoor Air Hygiene Commission www.umweltdaten.de/publikationen/fpdf-l/4113.pdf