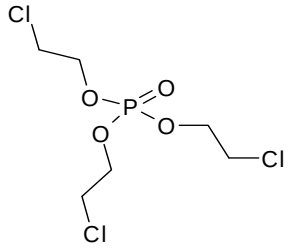
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-96-8
Chemical Name	Tris(2-chloroethyl)phosphate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Tris(2-chloroethyl)phosphate (TCEP) is well absorbed (> 90% of the dose) and distributed in rats after oral administration. High concentrations were found in liver and kidney 24 hours after administration and TCEP is thought to undergo enterohepatic circulation. The urinary metabolites were identical in rats and mice, and were mainly bis(2-chloroethyl) carboxymethylphosphate, bis(2-chloroethyl)hydrogen phosphate and bis(2-chloroethyl)-2-hydroxyethyl-phosphate glucuronide. Absorption data were not available for the dermal and inhalation route. Human data on toxicokinetics of TCEP were not available.

TCEP showed an oral LD_{50} for rats in the range of 430-1230 mg/kg bw. In rabbits, a dermal LD_{50} for 24-hours occlusive contact was in excess of 2150 mg/kg bw. In a limit inhalation test rats were exposed to a nominal concentration of 25.7 g/m^3 for 1 hour. The animals revealed moderate lacrymation and salivation; no mortality resulted.

In Draize tests, neat TCEP produced mild irritant reactions when in 24 hour occlusive contact with the skin of rabbits (test according to OECD Test Guideline (TG) 404). The neat liquid instilled into the eyes of rabbits produced mild conjunctival irritation (test according to OECD TG 405). No skin sensitizing potential of TCEP was detected in guinea pigs whose skin was in repeated contact with the neat liquid (Buehler Test). Since negative results obtained with a Buehler test are considered to be insufficient for an appropriate assessment of skin sensitizing potential, a read across approach was performed using relevant data of two other structurally related chloroalkyl phosphates: Tris(2-chloro-1-methylethyl) phosphate (TCPP) and Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP). The results of valid skin sensitisation studies on TCPP and TDCP did not show a significant skin sensitizing potential. Taking into account all sensitisation studies, it is concluded that TCEP should be non-sensitizing to humans.

Kidney and brain were the main sites of the toxic effects in experimental animals after repeated oral administration of TCEP (dose ranges from 22 to 700 mg/kg bw/d in rats and from 12 to 1500 mg/kg bw/d in mice). Increased liver weight was also observed in rats and mice but no overt liver toxicity could be identified or could be related to TCEP treatment. Kidneys appear to be the most sensitive organs for repeated exposure of TCEP. Degenerative lesions in the brain were only manifested at higher doses in the rat. The incidence and severity of the adverse kidney pathology was dose- and time-related, and the nature of the lesions (mainly involving the kidney tubules and consisting of hyperplasia, hypertrophy and karyomegaly) was similar in two strains of rat (Sprague-Dawley and F344/N) and two strains of mouse (B6C3F1 and Scl:ddY). No NOAEL could be identified in long-term studies. Similar kidney lesions were observed at the lowest tested oral doses of 192 mg/kg bw/d administered in the diet to male Sprague-Dawley rats for three months, of 44 mg/kg bw/d given by gavage to male and female F344/N rats for 103 weeks, of 175 mg/kg bw/ given by gavage to B6C3F1 mice for 103 weeks, and of 12 mg/kg bw/d administered in the diet of Scl:ddY mice for 18 months. Therefore, the critical LOAEL for kidney lesions is 12 mg/kg bw/d.

Orally administered TCEP induced a range of degenerative changes in the brain of rats: the incidence of these lesions was dose- and sex-related, and there was a clear time-response relationship in frequency and severity. Females were more susceptible than males. NOAELs for brain effects in rats from sub-chronic and chronic oral toxicity studies were in the range of 44 to 175 mg/kg bw/d. The NOAEL for the inhibition of serum cholinesterase activity that has only been reported in female rats was 88 mg/kg bw/d. In mice, oral doses of 350 mg/kg bw/d administered for 2 years produced no adverse brain pathology, and repeated oral doses up to 700 mg/kg bw/d had no effect on cholinesterase activity. Although several chlorinated alkyl phosphates have been shown to produce delayed neurotoxicity in hens (study according to OECD TG 418), an oral dose of 14200 mg TCEP /kg bw in hens did not cause behavioural effects or nerve damage suggestive of neurotoxicity.

No repeated dose studies on the dermal and the inhalation route were available.

In general, Ames tests in *S. typhimurium* (conducted according to OECD TG 471) provided no evidence of mutagenic potential. Gene mutations were not induced in mouse lymphoma and V79 cells in culture (OECD TG 476). There were no treatment-related increases either in chromosomal damage in CHO cells (OECD TG 473) or Unscheduled DNA Synthesis in human WI-38 cells (OECD TG 482). The small increases in Sister Chromatid Exchange seen at high TCEP concentrations in V79 cells in culture (OECD TG 479) were not considered to be a reliable indication of genotoxic potential. Two investigations (conducted according to OECD TG 474) of the induction of chromosome damage (micronuclei) in mice found no evidence of activity up to maximum tolerated doses. Overall, it is concluded that there is no convincing evidence that TCEP possesses genotoxic potential.

TCEP was carcinogenic in both sexes of rats and mice. It produced benign and malignant tumors in the kidney of rodents. These were seen in long-term studies in male and femaleF344/N rats at gavage doses ≥44 mg/kg bw/d, and in male B6C3F1 mice at 350 mg/kg bw/d; and in diet studies in male Scl:ddY mice at doses of 300 mg/kg bw/d and above. Dose-related increased incidences of hyperplasia and hypertrophy of the urinary tubule epithelium together with karyomegaly were also observed at doses of ≥44 mg/kg bw/d in male and female F344/N rats, at ≥175 mg/kg bw/d in male and female B6C3F1 mice, and at ≥12 mg/kg bw/d in male Scl:ddY mice. The value of 12 mg/kg bw/d is considered as the LOAEL for tumor formation. Since there was no evidence of a direct genotoxic mode of action, it can be assumed that the kidney tumours developed by a non-genotoxic (epigenetic) mechanism. If this is the case, the LOAEL for kidney toxicity would also be the LOAEL for kidney tumour formation. In addition to the kidney tumours, TCEP induced benign and malignant tumours in the liver of male Scl:ddY mice at 300 mg/kg bw/d and above, and in the Harderian gland of female B6C3F1 mice at ≥175 mg/kg bw/d. Again, since there was no evidence of a direct genotoxic mode of action, it could be assumed that that these tumour types are mediated by non-genotoxic (epigenetic) mechanisms and as such the tumour incidence dose-responses would exhibit thresholds. These threshold doses would be higher than that derived for the kidney carcinogenic action.

Significant impairment of reproductive capacity and fertility was seen in a continuous breeding study in which CD-1 mice received 300 or 700 mg/kg bw/d by gavage. No similar fertility effects were seen at 175 mg/kg bw/d (NOAEL for fertility). Supplementary studies indicated male mice were more sensitive to TCEP treatment than were the females. Mice given high oral doses exhibited reduced testes weights and sperm counts. In a study which provided limited information there was no evidence of development toxicity in Wistar rats which were given oral doses of 50, 100, or 200 mg/kg bw/d on gestation days 7 to 15. Adverse effects (skeletal variations) were noted at maternally toxic doses.

Environment

Tris(2-chloroethylphosphate) (TCEP) is a liquid (melting point: <-70 °C) with a water solubility of 7820 mg/l at 20 °C and a log Kow of 1.78. A vapour pressure of 0.00114 Pa at 20 °C was extrapolated from a measured value of 43 Pa at 137°C.

According to the fugacity model of Mackay (level 1), the main target compartment is the hydrosphere (94.8 %). The calculated Henry's law constant of $4.155 \cdot 10^{-5}$ Pa.m^3/mol at 20 °C indicates a low potential of volatilisation from water.

Hydrolysis does not contribute to the environmental degradation of TCEP ($t_{1/2} \approx 3980$ days). In the atmosphere, TCEP will react with photochemically produced hydroxyl radicals. Based upon atmospheric concentrations of 5 ·

10^5 OH/cm^3, the atmospheric half-life of TCEP has been estimated to be 17.5 hours. From the spectroscopic data available for TCEP, direct photolysis is not to be expected.

TCEP is non biodegradable (OECD 302 B: < 10 % after 27 d with industrial activated sludge as inoculum). The measured log Kow of 1.78 indicates a low potential for bioaccumulation. This was confirmed by experimentally determined BCF of 0.6 to 5 in various fish species (*Cyprinus carpio*, *Carassius auratus*, *Oryzias latipes*). The calculated Koc of 110 l/kg indicates a low potential for geoaccumulation.

Short-term tests are available for fish, invertebrates and algae. The lowest effect values from these tests were: *Carassius auratus*: 96h-LC_{50} = 90 mg/l; *Daphnia magna*: 24h-EC_{50} = 235 mg/l, *Scenedesmus subspicatus*: 72h-E_rC_{50} = 3.6mg/l, 72h-E_bC_{50} = 1.1mg/l (72h-E_rC_{10} = 0.55mg/l, 72h-E_bC_{10} = 0.2mg/l). In addition, a long-term test with *Daphnia magna* is available in which a 21d-NOEC of 13 mg/l was determined. Applying an assessment factor of 10 on the EC_{10} for algae, provides a PNECaqua of 65 µg/l.
For the terrestrial compartment tests with plants and invertebrates are available. For *Avena sativa* a 14d-EC_{50} of 64 mg/kg dw was determined. For the earthworm *Eisenia andrei* a 14d-LC_{50} > 1000 mg/kg dw was determined. In a long-term test with springtail (*Folsomia candida*), a 28d-EC_{10} of 19.3 mg/kg dw was determined for mortality. In a test on the inhibition of the dehydrogenase activity of soil microorganisms, both tested concentrations (5 and 50 mg/kg dw) caused effects in the sandy soil, but in the loamy soil only the higher concentration lead to an inhibition of the enzyme activity. A PNECsoil of 0.341 mg/kg dw was derived from the EC_{10} for *Folsomia* using an assessment factor of 50.

Exposure

In 1998, TCEP was produced in the European Union (EU) in quantities of about 2000 tons/annum. However, the situation changed recently; at present there is no production of TCEP in the EU. A quantity of 1007 tons was imported into the EU in 2002. TCEP is mainly used as flame retardant. In an effort by industry to substitute TCEP by other flame retardants the EU tonnage has been in decline during the last decade (EU tonnage in 1991/1992: 10500 t). The substitution by analogs was based on the carcinogenic properties of TCEP.

Main field of application is the polymer industry (~ 90 %). The products are used in the manufacture of cars, railways, aircrafts; other branches to use TCEP containing products are furniture, textile and building industry. About 5 % of the total volume is used in paints and varnishes (flame retardant). A further 5 % serve as an intermediate in the chemical industry.

Releases of TCEP into the environment are to be expected during production, formulation and processing via waste water and, to less extent, exhaust gases. Further releases are to be expected during use and service life of TCEP containing products (polymers, paints). If these are disposed at landfill sites, significant leaching may occur due to high solubility of TCEP.

There are no indications for any direct application of TCEP by consumers. However, due to the use as flame retardant in various materials exposure of consumers is possible. It has been shown that TCEP will be released from a number of sources which have been treated with flame retardants, namely timber, foam rubber, carpets, plastic materials, glues, and lacquers. The release occurs primarily by abrasion thus leading TCEP to become a constituent of dust (house dust and airborne dust).

Inhalation exposure takes place by inhaling airborne particles. Dermal exposure can occur by direct contact (with e.g. upholstery and furniture coverings). Oral exposure of TCEP by dust uptake may represent a significant source of exposure for children. A significant source of oral exposure of babies could be sucking on toys containing TCEP.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard for human health (repeated dose toxicity, potential of neurotoxicity, carcinogenicity, impairment of fertility, and potential for developmental toxicity). Based on the available exposure information, member countries are invited to perform an exposure assessment, and if

necessary a risk assessment for human health.

Note: A draft risk assessment performed in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints, especially for carcinogenicity. For workers as well as consumers (including babies), risk reduction measures are recommended in the EU. For TCEP, three occupational exposure scenarios are evaluated: production, use for the production of formulations and use of TCEP-containing formulations including spray application and applications without formation of aerosols. The overall result of occupational risk assessment indicates that current exposure levels (inhalation and dermal contact) are too high for all three exposure scenarios.

Environment: The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard for the environment (fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.
Note: A draft risk assessment for this chemical is currently under discussion in the EU in the context of the EU Regulation 793/93.