TRIS(2-CHLOROETHYL) PHOSPHATE

Data were last evaluated in IARC (1990).

1. Exposure Data

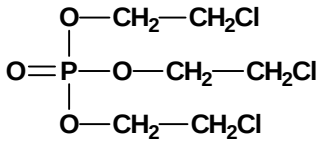
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 115-96-8

Systematic name: Tris(2-chloroethyl) phosphate

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_{12}Cl_3O_4P$ Relative molecular mass: 285.49

1.1.3 *Physical properties* (for details, see IARC, 1990)

(*a*) *Boiling-point*: 330°C

(*b*) *Melting-point*: –55°C

1.2 Production, use and human exposure

Tris(2-chloroethyl) phosphate is used as a flame retardant in plastics, especially in flexible foams used in automobiles and furniture, and in rigid foams used for building insulation. No data on occupational exposure levels were available. Tris(2-chloroethyl) phosphate has been detected in drinking-water, river water, sea water and sediments in various parts of the world (IARC, 1990).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Tris(2-chloroethyl) phosphate was tested for initiating and promoting activity and for complete carcinogenicity in one strain of mice by skin application. No initiating activity was found; promoting activity and complete carcinogenicity could not be evaluated (IARC, 1990).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 60 male and 60 female B6C3F_1 mice, eight to nine weeks of age, were administered 0, 175 or 350 mg/kg bw tris(2-chloroethyl) phosphate (purity, ≈ 98%) by gavage on five days per week for up to 104 weeks. Eight to ten mice of each sex from each group were evaluated at 66 weeks for organ weights and clinical pathology. There was no significant difference in survival between treated and control groups of either sex, and final mean body weights of mice were similar among all groups. The principal chemical-related effects occurred in the kidney, in which nuclear enlargement (karyomegaly) of tubule epithelial cells was present in approximately 80% of high-dose mice. In the original diagnosis, renal tubule adenomas were seen in one control male, one high-dose male and one low-dose female. A carcinoma was also seen in one high-dose male. In a subsequent examination of step sections of all the mouse kidneys, adenomas were found in one low-dose male and two high-dose males. The incidences of renal tubule neoplasms in the original and step sections combined were (control, low-dose, high-dose) 1/50, 1/50, and 4/50 for males. Treated female mice demonstrated a marginally increased incidence of neoplasms (primarily adenomas) of the Harderian gland (3/50, 8/50, 7/50); in addition, three Harderian gland neoplasms occurred in high-dose female mice evaluated after 66 weeks (United States National Toxicology Program, 1991).

3.1.2 *Rat*

Groups of 60 male and 60 female Fischer 344/N rats, eight to ten weeks of age, were administered 0, 44 or 88 mg/kg bw tris(2-chloroethyl) phosphate (purity, ≈ 98%) by gavage on five days per week for up to 104 weeks. Nine or ten rats of each sex from each group were evaluated at 66 weeks for organ weights and clinical pathology. There were no clinical signs attributable to the treatment. Survival in the high-dose groups of male and female rats was significantly reduced, so that, at two years, the survivors in the control, low- and high-dose groups, respectively, were: males—36/50, 33/50, 25/50; females—32/50, 33/50, 17/50. Female rats dying early or that were killed while moribund frequently had brain lesions, whereas male rats did not. Final mean body weights of surviving rats were similar to those of controls. All rats were examined microscopically. The principal treatment-related effects occurred in the kidney and brain. The incidences of focal hyperplasia of the renal tubule epithelium and renal tubule adenomas were markedly increased in male rats receiving 88 mg/kg tris(2-chloroethyl) phosphate and, to a lesser

extent, in female rats (control, low-dose, high-dose; renal tubule hyperplasia, male rats: 0/50, 2/50, 24/50; female rats: 0/50, 3/50,16/50; renal tubule adenoma, male rats: 1/50, 5/50, 24/50 ($p < 0.001$); female rats: 0/50, 2/50, 5/50) ($p = 0.003$)). Renal tubule carcinomas occurred in one control and one high-dose male rat. Degenerative lesions consisting of gliosis, mineralization, haemorrhage and/or haemosiderin accumulation occurred in the cerebrum and brain stem of more than 50% of female rats receiving 44 or 88 mg/kg bw tris(2-chloroethyl) phosphate; similar lesions were seen in only a few treated males (United States National Toxicology Program, 1991).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Neurotoxic effects of tris(2-chloroethyl) phosphate have been reported in rats and hens (IARC, 1990).

Neurotoxic effects were observed in 16-week dose-range finding studies preliminary to the carcinogenicity studies described in Section 3.1 (United States National Toxicology Program, 1991). Mild inhibition of serum cholinesterase activity was seen in female rats receiving 175 and 350 mg/kg bw for either 16 days or 16 weeks, but not in male rats or in male or female mice. Clinical signs of toxicity in female rats included ataxia, excessive salivation, gasping and convulsions, which may have been related to the cholinesterase inhibition. Alternatively, some of the clinical signs may be attributed to the observed neuronal necrosis in the hippocampus and thalamus. Female rats were also more seriously affected by neurotoxicity in the subsequent carcinogenicity study.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Tris(2-chloroethyl) phosphate was not mutagenic to bacteria in the absence of an exogenous metabolic system but gave equivocal results in the presence of an exogenous metabolic system (IARC, 1990). It caused cell transformation and, in single studies, sister chromatid exchanges but not chromosomal aberrations or mutations in rodent cells *in vitro*. In single studies, it gave equivocal results in a micronucleus test in Chinese hamsters and caused dominant lethal mutations in rats *in vivo*.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of tris(2-chloroethyl) phosphate were available.

There is *limited evidence* for the carcinogenicity of tris(2-chloroethyl) phosphate in experimental animals.

Overall evaluation

Tris(2-chloroethyl) phosphate is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

Galloway, S.W., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J, Margolin, B.H., Resnick, M.A., Anderson, B. & Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ. Mutag.*, **10** (Suppl. 10), 1–175

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutag*., **5** (Suppl. 1), 3–142

IARC (1990) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 48, *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry*, Lyon, pp. 109–120

Nakamura, A., Tateno, N., Kojima, S., Kaniwa, M.-A. & Kawamura, T. (1979) The mutagenicity of halogenated alkanols and their phosphoric acid esters for *Salmonella typhimurium. Mutat. Res*., **66**, 373–380

Prival, M.J., McCoy, E.C., Gutter, B. & Rosenkranz, H. (1977) Tris(2,3-dibromopropyl)-phosphate: mutagenicity of a widely used flame retardant. *Science*, **195**, 76–78

Sala, M., Gu, Z.G., Meons, G. & Chouroulinkov, I. (1982) In vivo and in vitro biological effects of the flame retardants tris(2,3-dibromopropyl)phosphate and tris(2-chloroethyl)ortho-phosphate. *Eur. J. Cancer*, **18**, 1337–1344

Shepel'skaia, N.R. & Dyshginevich, N.E. (1981) Experimental study of the gonadotoxic effect of tris(chloroethyl) phosphate. *Gig. Sanit.*, **6**, 20–21 (in Russian)

Table 1. Genetic and related effects of tris(2-chloroethyl) phosphate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	6950	Prival *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	(+)	1427	Nakamura *et al*. (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	6950	Prival *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	143	Nakamura *et al*. (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	6950	Prival *et al*. (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Haworth *et al*. (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	–	2000	Sala *et al*. (1982)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	+	700	Sala *et al*. (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	?	500	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	1600	Galloway *et al*. (1987)
TCM, Cell transformation, C3H 10T½ mouse cells	–	(+)	900	Sala *et al*. (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	400	Sala *et al*. (1982)
MVM, Micronucleus test, Chinese hamster lung V79 cells *in vivo*	?		250 ip × 1	Sala *et al*. (1982)
DLR, Dominant lethal test, rats *in vivo*	+		0.5 mg/m^3 inh	Shepel'skaia & Dyshginevich (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; inh, inhalation

United States National Toxicology Program (1991) *Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl)phosphate (CAS No.115-96-8) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies)* (Technical Report Series No. 391; NIH Publication No. 91-2846), Research Triangle Park, NC, United States Department of Health and Human Services