TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

1. Chemical and Physical Data

1.1 Synonyms

Tetrakis(hydroxymethyl) phosphonium sulfate

Chem. Abstr. Services Reg. No.: 55566-30-8

Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1) (salt)

IUPAC Systematic Name: Bis[tetrakis(hydroxymethyl) phosphonium] sulfate (salt)

Synonyms: Octakis(hydroxymethyl) phosphonium sulfate; THPS

Tetrakis(hydroxymethyl) phosphonium chloride

Chem. Abstr. Services Reg. No.: 124-64-1

Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, chloride

IUPAC Systematic Name: Tetrakis(hydroxymethyl) phosphonium chloride

Synonyms: Tetrahydroxymethylphosphonium chloride; THPC

Tetrakis(hydroxymethyl) phosphonium acetate/phosphate

Chem. Abstr. Services Reg. No.: 55818-96-7

Chem. Abstr. Name: Phosphonium, tetrakis(hydroxymethyl)-, acetate (salt), mixture with tetrakis(hydroxymethyl) phosphonium phosphate (3:1) (salt)

IUPAC Systematic Name: Tetrakis(hydroxymethyl) phosphonium acetate (salt), mixture with tris[tetrakis(hydroxymethyl) phosphonium] phosphate (salt)

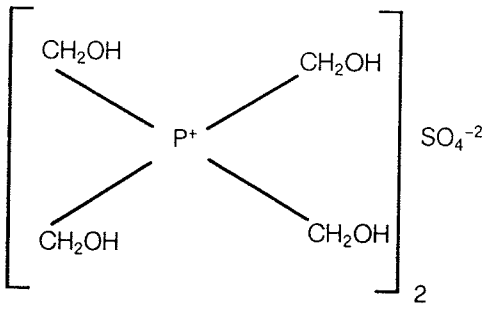
See Table 1 for CAS numbers and names of other tetrakis(hydroxymethyl) phosphonium salts.

Table 1. Chemical Abstracts Services Registry numbers of tetrakis(hydroxymethyl) phosphonium salts

Salt	CAS No.
Acetate	7580-37-2
Acetate-phosphate (1:1)	62588-94-7
Bromide	5940-69-2
6-Carboxycellulose salt	73082-49-2
Cellulose carboxymethyl ether salt	73083-23-5
Formate	25151-36-4
Hydroxybutanedioate	39734-92-4
2-Hydroxypropionate	39686-78-7
Iodide	69248-12-0
1-Naphthalenesulfonate	79481-21-3
2-Naphthalenesulfonate	79481-22-4
Oxalate (1:1)	53211-22-6
Oxalate (2:1)	52221-67-7
Phosphate	22031-17-0
Tetraphenylborate-tetraacetate	15652-65-0
para-Toluenesulfonate	75019-90-8

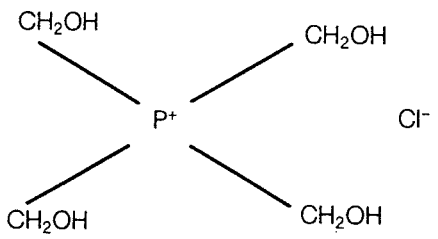
1.2 Structural and molecular formulae and molecular weights

Tetrakis(hydroxymethyl) phosphonium sulfate



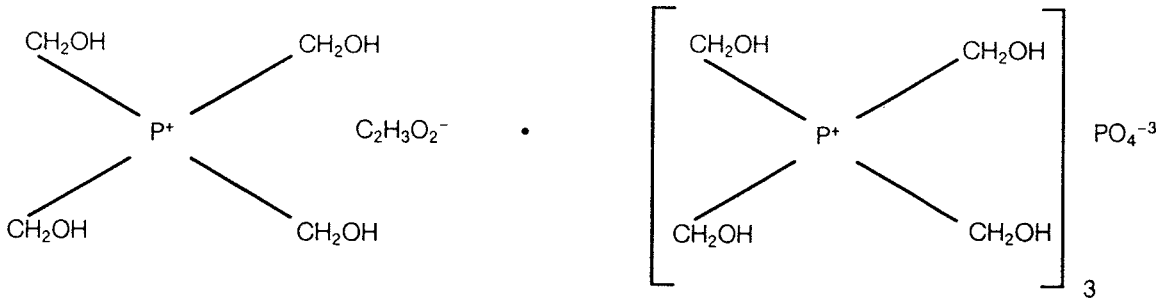
$C_8H_{24}O_{12}P_2S$ Mol. wt: 406.28

Tetrakis(hydroxymethyl) phosphonium chloride



$C_4H_{12}ClO_4P$ Mol. wt: 190.56

Tetrakis(hydroxymethyl) phosphonium acetate/phosphate



$C_4H_{12}O_4P \cdot C_2H_3O_2/(C_4H_{12}O_4P)_3 \cdot PO_4$ Mol. wt: 214.16/560.30

1.3 Chemical and physical properties of the pure substance

Tetrakis(hydroxymethyl) phosphonium sulfate

(*a*) *Description*: Crystalline solid (Weil, 1980)

(*b*) *Solubility*: Soluble in water (Weil, 1980)

Tetrakis(hydroxymethyl) phosphonium chloride

(*a*) *Description*: Crystalline solid (Weil, 1980)

(*b*) *Melting-point*: 154°C (Grasseli & Ritchey, 1975)

(*c*) *Spectroscopy data*: Infrared (prism [13510]; grating [47569P]), ultraviolet and nuclear magnetic resonance (proton [11664]) spectral data have been reported (Sadtler Research Laboratories, 1980; National Toxicology Program, 1987).

(*d*) *Solubility*: Soluble in water (Weil, 1980)

Tetrakis(hydroxymethyl) phosphonium acetate/phosphate

No data were available to the Working Group.

1.4 Technical products and impurities

Tetrakis(hydroxymethyl) phosphonium sulfate

Trade names: Pyroset TKO; Retardol S

Tetrakis(hydroxymethyl) phosphonium chloride

Trade names: Proban CC; Pyroset TKC; Retardol C

Tetrakis(hydroxymethyl) phosphonium acetate/phosphate

Trade names: Pyroset Flame Retardant TKP; Pyroset TKP

Tetrakis(hydroxymethyl) phosphonium chloride (THPC) and tetrakis(hydroxymethyl) phosphonium sulfate (THPS) are marketed in concentrated aqueous solutions at approximately 80 and 75 wt%, respectively (Albright & Wilson Americas, Inc., 1988a,b). Commercial THPC has been reported to contain free formaldehyde (see IARC, 1982; 3.8% at the pH at which THPS is available, pH 0.4; Ulsamer *et al.*, 1980). Tetrakis(hydroxymethyl) phospho-

nium acetate/phosphate (THPA/P) was available in the USA as a clear, nearly colourless solution with a pH of approximately 5, containing 10% active phosphorus (Hooper *et al.*, 1976a).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Tetrakis(hydroxymethyl) phosphonium salts have been produced for commercial use since the 1950s. The first, THPC, was introduced in 1953. The salts are produced by the reaction of formaldehyde with phosphine in the appropriate aqueous acid (Weil, 1980; Hawley, 1981).

Two US companies supply THPS and THPC. Combined annual use of each compound in the USA is 900-4500 tonnes (National Toxicology Program, 1987).

(*b*) *Use*

Tetrakis(hydroxymethyl) phosphonium salts are used to produce crease-resistant flame-retardant finishes on cotton textiles and cellulosic fabrics (Hooper, 1973; Hooper *et al.*, 1976a,b). THPC, THPS and THPA/P can be cured on the fabric with amine compounds (e.g., ammonia, urea, melamine-formaldehyde resins) to form durable, cross-linked flame-retardant resin finishes (Weil, 1980). Recently, THPS has largely replaced THPC in commercial use (Duffy, 1983); THPA/P has never been a major commercial product. Many co-reactants have been used to form flame-retardant finishes with these compounds. One of the most popular processes has been the tetrakis(hydroxymethyl) phosphonium hydroxide-ammonia finish, in which THPS is converted to a free organic base and then cured on the fabric by reaction with ammonia gas (Weil, 1980).

In 1974, over 14 million metres of cotton flannel for children's nightwear were estimated to have been treated with tetrakis(hydroxymethyl) phosphonium salts in the USA (Hooper *et al.*, 1976a).

(*c*) *Regulatory status and guidelines*

No regulatory standard or guideline has been established for tetrakis(hydroxymethyl) phosphonium salts.

2.2 Occurrence

(*a*) *Natural occurrence*

These compounds are not known to occur as natural products.

(*b*) *Occupational exposure*

Approximately 100 workers were potentially exposed to THPC in the USA in 1972-74 (National Institute for Occupational Safety and Health, 1977).

No data on levels of exposure were available to the Working Group.

2.3 Analysis

A number of analytical methods have been used to identify and characterize THPC-based flame-retardant polymers on fabric. These include potassium iodate-thiosulfate titration (Frank, 1977), thermogravimetric and differential thermal analysis, differential scanning calorimetry, scanning and transmission electron microscopy, electron spin resonance and energy dispersive X-ray analysis (Frank *et al.*, 1982).

No data were available to the Working Group on methods for the analysis of tetrakis(hydroxymethyl) phosphonium salts in the workplace or in the environment.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Tetrakis(hydroxymethyl) phosphonium sulfate

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, seven weeks of age, received 0, 5 or 10 mg/kg bw THPS dissolved in distilled water (72:28 vol%) by gavage on five days a week for 104 weeks; all survivors were killed at 112 weeks of age. No difference in survival or mean body weight was observed between control and treated mice. The incidence of malignant lymphomas in males showed a negative trend: control, 2/50; low-dose, 9/50; high-dose, 0/50 (National Toxicology Program, 1987).

Rat: Groups of 49 or 50 male and female Fischer 344/N rats, six weeks of age, received 0, 5 or 10 mg/kg bw THPS in distilled water (72:28 vol%) by gavage on five days a week for 104 weeks. All survivors were killed at 112 weeks of age. Survival of treated males was reduced as compared to controls; mean body weights of treated animals were comparable to those of controls. The incidence of mononuclear-cell leukaemia in males showed a negative trend: control, 30/50; low-dose, 36/50; high-dose, 20/50 (National Toxicology Program, 1987).

Tetrakis(hydroxymethyl) phosphonium chloride

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight weeks of age, received 0, 7.5 or 15 (males) and 0, 15 or 30 (females) mg/kg bw THPC dissolved in deionized water (75:25 vol%) by gavage on five days a week for 103 weeks; all survivors were killed at 112-113 weeks of age. No difference in survival or in mean body weight was observed between control and treated mice. There was no significant increase in the incidence of any tumour in any organ in treated mice of either sex (National Toxicology Program, 1987).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, received 0, 3.5 or 7.5 mg/kg bw THPC in deionized water (75:25 vol%) by gavage on five days a week for 103 weeks; all survivors were killed at 111 weeks of age. Survival of high-dose females after week 70 was lower than that of controls; mean body weights of treated animals were comparable to those of controls. The incidence of mononuclear-cell leukaemia in males showed a negative trend: control, 19/50; low-dose, 25/50; high-dose, 16/50 (National Toxicology Program, 1987).

(*b*) *Skin application*

Mouse: Groups of 20 female ICR/Ha Swiss mice, six to eight weeks of age, received skin applications of 2 mg/mouse THPC in dimethyl sulfoxide (DMSO) to examine the initiating (I), promoting (II) and complete carcinogenic (III) potential in skin carcinogenesis. Two groups of 20 mice (I) received a single application of THPC in DMSO followed by applications of 2.5 μg/animal phorbol myristyl acetate (TPA) in acetone or acetone alone three times a week for 57 weeks. No skin tumour occurred in either group. Three groups of 20 mice (II) received a single application of 20 μg 7,12-dimethylbenz[*a*]anthracene in acetone followed by applications of either 2 mg/animal THPC in DMSO, 2.5 μg/animal TPA in acetone (positive control) or DMSO alone three times a week for 57 weeks. The numbers of mice with squamous-cell papillomas and carcinomas of the skin were 3/20 (three with a carcinoma [$p > 0.05$]), 19/20 (nine with a carcinoma) and 0/20, respectively. A further group of mice (III) received applications of 2 mg/animal THPC in DMSO alone three times a week for 57 weeks; one squamous-cell carcinoma of the skin developed, whereas no skin tumour was observed in an untreated group (Loewengart & Van Duuren, 1977).

A group of 60 female ICR/Ha Swiss mice, six to eight weeks of age, received skin applications of 2 mg/mouse THPC in acetone three times a week for 71 weeks. Control groups of 249 and 29 mice (effective numbers necropsied) received no treatment and treatment with 0.1 ml acetone, respectively. The numbers of mice with papillary tumours of the lung were 90/249 (36%), 7/29 (24%) and 17/59 (29%) in the two control and the THPC-treated groups, respectively; the numbers with papillomas of the forestomach were 6/249 (2%) and 1/59 (2%) in the untreated control and the treated groups, respectively (Van Duuren *et al.*, 1978).

Tetrakis(hydroxymethyl) phosphonium acetate/phosphate

Skin application

Mouse: In a two-stage carcinogenicity study, groups of 20 female ICR/Ha Swiss mice, six to eight weeks of age, received a single application of 20 μg 7,12-dimethylbenz[*a*]anthracene in acetone followed by applications of 7 mg/animal Pyroset TKP (THPA/P), 2.5 μg/animal TPA (positive control) or acetone three times a week for 57 weeks. The numbers of mice with squamous-cell papillomas and carcinomas of the skin in the THPA/P-, TPA- and acetone-treated groups were 7/20 (two with a carcinoma [$p = 0.004$]), 19/20 (nine with a carcinoma) and 0/20, respectively. When THPA/P was given alone, no skin tumour was observed (Loewengart & Van Duuren, 1977).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

No data were available to the Working Group.

(ii) *Toxic effects*

Tetrakis(hydroxymethyl) phosphonium sulfate

Administration by gavage of 2-50 mg/kg bw per day THPS in saline to male ICR Swiss mice for 14 days resulted in deaths in the group given 50 mg/kg bw after the fifth day. Application of 125-1000 mg/kg bw per day THPS to chemically depilated back skin of male ICR Swiss mice daily for up to 14 days resulted in reduced body weight, paralysis and superficial necrosis of the treated area at doses of 700 mg/kg and above (Connor *et al.*, 1980).

In gavage studies, Fischer 344/N rats and B6C3F$_1$ mice received single doses of 200-1600 mg/kg bw THPS; all rats at the highest dose and all mice receiving 400 mg/kg bw or more died. All rats and 8/10 mice that received doses of 100 mg/kg bw per day for 14 days died. Of animals dosed for 90 days on five days per week, male rats died after doses of 60 mg/kg bw per day and mice of each sex after 40 mg/kg bw per day or higher. In the last studies, hepatocyte vacuolar degeneration, which appeared to be related to treatment, was seen at doses of 10 mg/kg per day and above in rats and at 20 mg/kg per day and above in mice (National Toxicology Program, 1987).

In two-year studies (see also section 3.1), non-neoplastic lesions attributed to administration of THPS in rats included cystic degeneration of the liver in males and hepatocyte cytoplasmic vacuolization in animals of each sex. No significant non-neoplastic lesion attributable to the treatment was seen in mice (National Toxicology Program, 1987).

Tetrakis(hydroxymethyl) phosphonium chloride

The oral LD_{50} for THPC was reported to be 282 mg/kg bw in male rats (Ulsamer *et al.*, 1980). The compound was irritating to rats and rabbits following dermal application, and daily dermal exposures to a 30% solution were fatal to rats nine days after the first dose (Aoyama, 1975).

In gavage studies, all Fischer 344/N rats and B6C3F$_1$ mice that received single doses of 150 mg/kg bw and 300 mg/kg bw THPC, respectively, died. In 14-day studies, deaths were observed in rats that received 75 mg/kg bw and in mice that received 300 mg/kg bw. Deaths also occurred in 90-day studies in rats that received 15 mg/kg bw and in mice that received 135 mg/kg bw per day on five days a week. In the last studies, clinical signs of neurotoxicity and hepatocellular necrosis and vacuolization were seen in rats and mice (National Toxicology Program, 1987).

In two-year studies (see also section 3.1), non-neoplastic lesions in mice and rats treated with THPC included hepatocyte cytoplasmic vacuolization in animals of each sex, cystic degeneration of the liver in male rats, haematopoiesis of the spleen in female rats and follicular-cell hyperplasia of the thyroid in female mice (National Toxicology Program, 1987).

THPC reacts *in vitro* with the 2-amino group of guanosine to form a stable product (Loewengart & Van Duuren, 1976).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects* (see Appendix 1)

Tetrakis(hydroxymethyl) phosphonium sulfate

THPS was not mutagenic to several strains of *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system from Aroclor 1254-induced rat liver (Connor *et al.*, 1980; MacGregor *et al.*, 1980). Negative results in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were also obtained in mutagenicity assays performed on 200-μl samples of urine from male ICR Swiss mice treated with THPS by gavage (2 mg/kg bw or 50 mg/kg bw for 14 days, 50 mg/kg bw for five days) or by dermal application (125-1000 mg/kg bw, 13-16 days) or by feeding several doses of a cotton fabric treated with THPS and mixed in the diet over 14 days. These assays were conducted in the absence of exogenous metabolic activation and in the presence or absence of β-glucuronidase (Connor *et al.*, 1980).

THPS caused mutation at the TK locus in L5178Y mouse lymphoma cells in culture at 5 μg/ml in the absence of an exogenous metabolic system (National Toxicology Program, 1987).

This compound did not induce micronuclei in bone marrow of male ICR Swiss mice treated dermally. A two-fold increase in the incidence of chromatid breaks was seen, however, in bone marrow of mice treated orally with 10 mg/kg bw THPS, and a six-fold increase in polyploidy was seen in mice treated dermally with 1 g/kg (Connor *et al.*, 1980).

Tetrakis(hydroxymethyl) phosphonium chloride

THPC was not mutagenic to several strains of *S. typhimurium* in the presence or absence of an exogenous metabolic system from Aroclor 1254-induced rat liver (MacGregor *et al.*, 1980; National Toxicology Program, 1987) or Syrian hamster liver (National Toxicology Program, 1987).

The compound caused mutation at the TK locus in L5178Y mouse lymphoma cells at 5 μg/ml in the absence of an exogenous metabolic system (National Toxicology Program, 1987).

THPC induced sister chromatid exchange in the Chinese hamster CHO cell line in the presence and absence of an exogenous metabolic activation system from Aroclor 1254-induced rat liver at doses of 20 and 15 μg/ml (National Toxicology Program, 1987) and 40 and 50 μg/ml (Loveday *et al.*, 1989), respectively. It induced chromosomal aberrations in the CHO cell line, in the presence and absence of an exogenous metabolic system from Aroclor 1254-induced rat liver at 50 and 30 μg/ml, respectively (National Toxicology Program, 1987). In the absence of an exogenous metabolic system, it induced chromosomal aberrations in CHO cells at 30-50 μg/ml (Loveday *et al.*, 1989), in Chinese hamster lung cells at 30 μg/ml (Ishidate, 1983) and in the Chinese hamster DON cell line at 19 μg/ml (Sasaki *et al.*, 1980).

DMSO extracts of fabrics that had been treated with either THPS or THPC induced ouabain resistance in the Chinese hamster V79 cell line, in the presence and absence of an exogenous metabolic system from Aroclor 1254-induced rat liver, and cell transformation in mouse BALB/c 3T3 cells (Ehrlich *et al.*, 1980).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Tetrakis(hydroxymethyl) phosphonium salts are used to produce crease-resistant and flame-retardant finishes on textile fabrics, including children's nightwear. No data on occupational exposure levels were available.

4.2 Experimental carcinogenicity data

Tetrakis(hydroxymethyl) phosphonium sulfate was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats. No dose-related increase in the incidence of any tumour was observed, but in males receiving the low dose there was an increased incidence of malignant lymphomas in mice and of mononuclear-cell leukaemia in rats.

Tetrakis(hydroxymethyl) phosphonium chloride was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats. No dose-related increase in the incidence of any tumour was observed; however, in male rats receiving the low dose there was an increased incidence of mononuclear-cell leukaemia. Tetrakis(hydroxymethyl) phosphonium chloride did not show significant promoting activity in a two-stage skin carcinogenicity test in mice.

A mixed acetate/phosphate salt of tetrakis(hydroxymethyl) phosphonium base showed weak promoting activity in a two-stage skin carcinogenicity study.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In single studies, tetrakis(hydroxymethyl) phosphonium sulfate did not induce micronuclei but caused a marginal increase in the frequency of chromosomal aberrations in mouse bone marrow *in vivo* and induced mutation in mouse cells *in vitro*. It was not mutagenic to bacteria either in the presence or absence of an exogenous metabolic system.

Summary table of genetic and related effects of tetrakis(hydroxymethyl) phosphonium chloride

Nonmammalian systems													**Mammalian systems**																												
Prokaryotes		Lower eukaryotes				Plants			Insects				*In vitro*												*In vivo*															
													Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	-													+[1]	+		+																								

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

- \- considered to be negative
- +[1] considered to be positive, but only one valid study was available to the Working Group
- \+ considered to be positive for the specific endpoint and level of biological complexity

Summary table of genetic and related effects of tetrakis(hydroxymethyl) phosphonium sulfate

Nonmammalian systems													**Mammalian systems**																									
Proka-ryotes		Lower eukaryotes				Plants			Insects				*In vitro*												*In vivo*													
													Animal cells								Human cells								Animals							Humans				
D	G	D	R	G	A	D	G	C	R	G	C	A	D	G	S	M	C	A	T	I	D	G	S	M	C	A	T	I	D	G	S	M	C	DL	A	D	S	M	C	A
	-													$+^1$																		$-^1$	$+^1$								

A, aneuploidy; C, chromosomal aberrations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation

In completing the tables, the following symbols indicate the consensus of the Working Group with regard to the results for each endpoint:

- \- considered to be negative
- $+^1$ considered to be positive, but only one valid study was available to the Working Group.
- $-^1$ considered to be negative, but only one valid study was available to the Working Group

Tetrakis(hydroxymethyl) phosphonium chloride induced sister chromatid exchange and chromosomal aberrations in Chinese hamster cells *in vitro* and, in a single study, mutation in mouse cells *in vitro*. It was not mutagenic to bacteria either in the presence or absence of an exogenous metabolic system.

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of tetrakis(hydroxymethyl) phosphonium salts in experimental animals.

No data were available from studies in humans on the carcinogenicity of tetrakis-(hydroxymethyl) phosphonium salts.

Overall evaluation

Tetrakis(hydroxymethyl) phosphonium salts *are not classifiable as to their carcinogenicity to humans (Group 3)*.

5. References

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[1]For description of the italicized terms and criteria for making the evaluation, see Preamble, pp. 25–29.

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