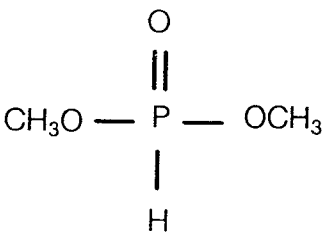
DIMETHYL HYDROGEN PHOSPHITE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 868-85-9
Chem. Abstr. Name: Dimethyl phosphonate
IUPAC Systematic Name: Dimethyl phosphonate
Synonyms: Bis(hydroxymethyl)phosphine oxide; dimethoxyphosphine oxide; dimethyl phosphite; dimethyl acid phosphite; *O,O*-dimethyl phosphonate; dimethyl phosphorous acid; DMHP; hydrogen dimethyl phosphite; methyl phosphonate; phosphorous acid dimethyl ester

1.2 Structural and molecular formulae and molecular weight



$C_2H_7O_3P$ Mol. wt: 110.05

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with mild odour (Hawley, 1981)

(*b*) *Boiling-point*: 170-171°C (Weast & Astle, 1985)

(*c*) *Density*: 1.2004 at 20°C (Weast & Astle, 1985)

(*d*) *Spectroscopic data*: Infrared (prism, Sadtler [3003, 61328], Aldrich [549D]; prism-FT [912D]; grating [42253P], nuclear magnetic resonance (proton, Sadtler [6652], Aldrich [864C]; C-13 [529]) and ultraviolet spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983; National Toxicology Program, 1985; Pouchert, 1985).

(*e*) *Solubility*: Soluble in water; miscible with most common organic solvents (Hawley, 1981)

(*f*) *Volatility*: Vapour pressure, < 1.0 mm Hg at 20°C (Albright & Wilson Americas, 1987)

(*g*) *Flash-point*: 96°C (Hawley, 1981)

(*h*) *Reactivity*: Hydrolyses in water with a half-life of approximately ten days at 25°C and 19 days at 20°C; basic conditions accelerate hydrolysis (TOXNET, 1988)

(*i*) *Conversion factor*: $mg/m^3 = 4.5 \times ppm$[1]

1.4 Technical products and impurities

Trade name: TL 585

Commercial dimethyl hydrogen phosphite is marketed as a high-purity liquid (99%) for industrial use. Trace levels of dimethyl methyl phosphonate, trimethyl phosphate and methanol have been reported in the technical product (Albright & Wilson Americas, 1987).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Dimethyl hydrogen phosphite is manufactured by the reaction of phosphorous trichloride with methanol or with sodium methoxide (US Environmental Protection Agency, 1985).

Between 95 and 950 thousand tonnes of dimethyl hydrogen phosphite were produced or imported in the USA in 1977, when two companies reported production and one reported importation of the compound (US Environmental Protection Agency, 1985). More recently, two manufacturers have been identified in the UK and one each in Canada, France, the Federal Republic of Germany, Switzerland (SRI International, 1986) and the USA (US International Trade Commission, 1988).

(*b*) *Use*

Dimethyl hydrogen phosphite is used as a flame retardant on Nylon 6 fibres (see IARC, 1979) and, in combination with guanidine and formaldehyde (see IARC, 1982), to impart flame and crease resistance to cotton textiles. The compound is also used to increase fire resistance to cellulosic textiles, acrolein-grafted polyamide fibres and γ-irradiated polyethylene. It is used as a lubricant additive, as a chemical intermediate in the production of organophosphorous pesticides and as an adhesive. Dimethyl hydrogen phosphite has also been used as a stabilizer in oil and plaster and, in combination with pyrocatechol, as a corrosion

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[1]Calculated from mg/m^3 = (molecular weight/24.45) x ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

inhibitor on steel (Hawley, 1981; National Toxicology Program, 1985; US Environmental Protection Agency, 1985).

(*c*) *Regulatory status and guidelines*

No regulatory standard or guideline has been established for dimethyl hydrogen phosphite.

2.2 Occurrence

(*a*) *Natural occurrence*

Dimethyl hydrogen phosphite is not known to occur as a natural product.

(*b*) *Occupational exposure*

No data were available to the Working Group.

(*c*) *Other*

Dimethyl hydrogen phosphite is a degradation product of the pesticides trichlorphon and malathion and may be released into the environment following their application. It is a contaminant (approximately 2%) in the chemical intermediate trimethyl phosphite, which hydrolyses readily to dimethyl hydrogen phosphite in the presence of moist air or water (US Environmental Protection Agency, 1985).

2.3 Analysis

No data were available to the Working Group on methods for the analysis of dimethyl hydrogen phosphite in the workplace or the environment. Capillary gas chromatography and high-performance liquid chromatography have been used to analyse this compound under conditions simulating a physiological environment (Nomeir *et al.*, 1988).

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

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, six to eight weeks of age, were administered 0, 100 or 200 mg/kg bw dimethyl hydrogen phosphite (purity, >97-98%) dissolved in corn oil by gavage on five days a weeks for 103 weeks. All survivors were killed at 110-112 weeks of age. Survival of high-dose males was significantly shorter and mean body weights of high-dose males lower than those of vehicle controls. Hepatocellular adenomas

were observed in 0/50 female controls and in 6/49 at the low dose and 3/50 at the high dose (trend not significant). No other tumour was observed that could be attributed to treatment (National Toxicology Program, 1985; Dunnick *et al.*, 1986).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were administered 0, 100 or 200 (males) and 0, 50 or 100 (females) mg/kg bw dimethyl hydrogen phosphite (purity, >97-98%) dissolved in corn oil by gavage on five days a week for 103 weeks. All survivors were killed at 111 weeks of age. Survival of high-dose males was significantly shorter and mean body weights of high-dose males lower than those of vehicle controls. The incidences of squamous-cell carcinomas of the lung in males were 0/50 controls, 0/50 low-dose and 5/50 high-dose animals ($p = 0.034$, incidental tumour test for trend). The incidences of alveolar/bronchiolar carcinomas were significantly increased in males: controls, 0/50; low-dose animals, 1/50; high-dose animals, 20/50 ($p < 0.001$, incidental tumour test for trend). Alveolar/bronchiolar carcinomas were also observed in 0/50 female controls, and 1/49 at the low dose and 3/50 at the high dose ($p = 0.047$, incidental tumour test for trend. The combined incidences of squamous-cell papillomas and carcinomas of the forestomach were significantly increased in males: controls, 0/50; low-dose, 1/50; high-dose, 6/50 ($p = 0.006$, incidental tumour test for trend; National Toxicology Program, 1985; Dunnick *et al.*, 1986).

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*

The acute oral LD_{50}s for dimethyl hydrogen phosphite were 3283 and 3040 mg/kg bw for male and female Fischer 344/N rats, respectively, and 2815 mg/kg bw for male B6C3F$_1$ mice. In 15-day gavage studies, deaths of male and female rats occurred at 500 mg/kg bw and above, and deaths of male and female mice occurred at 2000 mg/kg bw and above. Gastritis, epithelial ulceration and squamous atrophy of the stomach appeared to be related to treatment in mice (National Toxicology Program, 1985).

In 90-day studies in which Fischer 344/N rats were administered 25-400 mg/kg bw dimethyl hydrogen phosphite by gavage (five days per week), deaths occurred at 400 and 200 mg/kg bw. Urinary bladder calculi were seen in two of ten high-dose males. In B6C3F$_1$ mice administered 95-1500 mg/kg bw dimethyl hydrogen phosphite by gavage, deaths occurred at concentrations of 375 mg/kg bw and above. Mice showed increased hepatocellular vacuolization, cardiac mineralization, testicular atrophy and lung congestion, which may have been related to treatment (National Toxicology Program, 1985).

Non-neoplastic lesions observed in two-year studies in rats (see also section 3.1) included alveolar epithelial hyperplasia, adenomatous hyperplasia of the lung and chronic interstitial chemical pneumonia in animals of each sex, as well as hyperkeratosis of the forestomach in high-dose males and hyperplasia of the forestomach in treated males and high-dose

females. In mice, focal calcification of the testis was associated with administration of dimethyl hydrogen phosphite (National Toxicology Program, 1985).

A dose of 200 mg/kg bw dimethyl hydrogen phosphite was administered in corn oil to male Fischer 344/N rats by gavage for up to six weeks to evaluate early microscopic and biochemical changes related to the lung and forestomach lesions noted in the two-year study (section 3.1). No lung change was seen, but epithelial hyperplasia, hyperkeratosis, subepithelial inflammation and submucosal oedema were observed microscopically in the forestomach. Levels of serum angiotensin converting enzyme (an indicator of lung injury) were elevated in treated rats from week 4 onwards but returned to control levels when treatment was stopped. Levels of soluble nonprotein sulfhydryls in the forestomach were elevated; a similar effect was produced by a single oral or intravenous administration of 1000 mg/kg bw. Microsomal cytochrome P450 activity in liver and kidney was unchanged, as were the activities of *para*-nitroanisole demethylase, soluble superoxide dismutase and glutathione *S*-transferase in liver, kidney, lung, forestomach and glandular stomach (Nomeir & Uraih, 1988).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

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

Dimethyl hydrogen phosphite 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 or Syrian hamster liver. It did not induce sex-linked recessive mutation in *Drosophila melanogaster* after feeding or injection (National Toxicology Program, 1985). It was reported not to induce unscheduled DNA synthesis in a primary culture of rat hepatocytes [details not given] (Tennant *et al.*, 1987a). It induced mutation at the TK locus in L5178Y mouse lymphoma cells in culture; an exogenous metabolic system from Aroclor 1254-induced rat liver was not required for activity but increased the response (McGregor *et al.*, 1988). It caused sister chromatid exchange and chromosomal aberrations in the Chinese hamster CHO cell line, both in the presence and absence of an exogenous metabolic system from Aroclor 1254-induced rat liver (Tennant *et al.*, 1987b).

(*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

Dimethyl hydrogen phosphite is used as a flame retardant on Nylon 6 fibres, as a chemical intermediate in the production of pesticides and in lubricant additives and adhesives. No data on occupational exposure levels were available. A potential source of exposure to this chemical is from its occurrence as a degradation product of the chemical intermediate trimethyl phosphite and of pesticides such as trichlorphon and malathion.

4.2 Experimental carcinogenicity data

Dimethyl hydrogen phosphite was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats. In rats, it caused an increase in the incidence of alveolar/bronchiolar carcinomas in animals of each sex and of squamous-cell carcinomas of the lung and of papillomas and carcinomas of the forestomach in males.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In single studies, dimethyl hydrogen phosphite induced sister chromatid exchange and chromosomal aberrations in Chinese hamster cells in culture and mutations in mouse cells in culture but did not induce sex-linked recessive lethal mutation in *Drosophila*. It was not mutagenic to bacteria in the presence or absence of an exogenous metabolic system.

4.5 Evaluation[1]

There is *limited evidence* for the carcinogenicity of dimethyl hydrogen phosphite in experimental animals.

No data were available from studies in humans on the carcinogenicity of dimethyl hydrogen phosphite.

Overall evaluation

Dimethyl hydrogen phosphite is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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

Summary table of genetic and related effects of dimethyl hydrogen phosphite

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
	$-^1$									$-^1$				$+^1$	$+^1$		$+^1$																									

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:

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

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

5. References

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