IARC MONOGRAPHS

ANTHRACENE, 2-BROMOPROPANE, BUTYL METHACRYLATE, AND DIMETHYL HYDROGEN PHOSPHITE

VOLUME 133

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 28 February to 7 March 2023

LYON, FRANCE - 2024

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

DIMETHYL HYDROGEN PHOSPHITE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 868-85-9 (IARC, 1990; Royal Society of Chemistry, 2022)

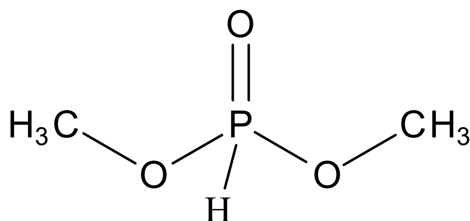
EC/List No.: 212-783-8 (ECHA, 2022)

IUPAC systematic name: dimethyl phosphonate (IARC, 1990; Royal Society of Chemistry, 2022)

Synonyms: dimethyl acid phosphite; phosphonic acid, dimethyl ester; dimethyl phosphite; bis(hydroxymethyl)phosphine oxide; DMHP; TL 585; hydrogen dimethyl phosphite; *O,O*-dimethyl phosphonate; dimethoxyphosphine oxide; phosphorous acid dimethyl ester (IARC, 1990; NCBI, 2022; Royal Society of Chemistry, 2022).

1.1.2 Structural and molecular information

Chemical structure:



Molecular formula: $C_2H_7O_3P$ (IARC, 1990; Royal Society of Chemistry, 2022)

Relative molecular mass: 110.05 (IARC, 1990).

1.1.3 Chemical and physical properties

Description: colourless liquid with mild odour (IARC, 1990)

Boiling-point: 170–171 °C (IARC, 1990; Royal Society of Chemistry, 2022)

Melting-point: less than −60 °C (OECD, 2004; Royal Society of Chemistry, 2022)

Flash-point: 70 °C at 101.3 kPa (OECD, 2004; ECHA, 2022; Royal Society of Chemistry, 2022)

Density: 1.2 g/mL (IARC, 1990; Royal Society of Chemistry, 2022)

Vapour pressure: 1.35 hPa at 20 °C (IFA, 2022a)

Solubility: soluble in water; miscible with most organic solvents (IARC, 1990)

Octanol/water partition coefficient (P): log K_{ow} = −1.2 (OECD, 2004; Royal Society of Chemistry, 2022)

Stability: hydrolyses in water with a half-life of ~10 days at 25 °C and 19 days at 20 °C; basic conditions accelerate hydrolysis (IARC, 1990).

[The Working Group used a conversion factor of 1 ppm ≈ 4.5 mg/m³ at 20 °C and 1.013 hPa (IARC, 1990).]

1.1.4 Technical grade and impurities

Dimethyl hydrogen phosphite of high purity (~99%) is available commercially from several vendors. Trace levels of monomethyl phosphonate, dimethyl methyl phosphonate, trimethyl phosphate, and methanol have been reported in the technical product (OECD, 2004; IARC, 1990).

1.2 Production and use

1.2.1 Production process

Dimethyl hydrogen phosphite is manufactured by the reaction of phosphorous trichloride with methanol or with sodium methoxide (IARC, 1990). Methyl chloride can be used as a catalyst (NCBI, 2022). It can also be synthesized by heating diethyl phosphite in methanol (Balint et al., 2013).

1.2.2 Production volume

The global production capacity for dimethyl hydrogen phosphite was estimated to be 3000–15 000 tonnes for about 10 producers in 2002, with an estimated production of 1000–5000 tonnes in each of western Europe, USA, and the rest of the world (OECD, 2004).

Dimethyl hydrogen phosphite is listed as a High Production Volume chemical; more than 1 million pounds [450 tonnes] were produced or imported into the USA in 1990 and 1994. The aggregated production volume of this chemical in the USA was reported as 500 000 to 1 million pounds [230–450 tonnes] in 2013 and 2014 (US EPA, 2016), 1 to 10 million pounds [450–4500 tonnes] in 2016 and 2017, and 1 to 2 million pounds [4500–9100 tonnes] in 2018 and 2019 (NCBI, 2022).

Since 2002, dimethyl hydrogen phosphite has been manufactured on an industrial scale in western Europe only at a single chemical plant in Leverkusen, Germany (OECD, 2004). Dimethyl hydrogen phosphite is also produced in China (Chemical Book, 2022). [The Working Group noted that the number of manufacturers varies according to different sources.]

1.2.3 Uses

Dimethyl hydrogen phosphite is used as an intermediate in the manufacture of adhesives, lubricants, organophosphate pesticides, and herbicides (such as glyphosate), as a stabilizer in oil and plaster, as a steel corrosion inhibitor in combination with pyrocatechol, and in pharmaceuticals (α-aminophosphonates, which are medicinally important phosphorus analogues of amino acids) (OECD, 2004; Varga & Keglevich, 2021; NCBI, 2022).

Dimethyl hydrogen phosphite is used as a reactive flame retardant (in combination with guanidine and formaldehyde) in textile finishing (IARC, 1990; OECD, 2004). It is also used to increase fire resistance in cellulosic textiles, acrolein-grafted polyamide fibres, and gamma-irradiated polyethylene (NCBI, 2022).

Dimethyl hydrogen phosphite can be converted by chemical synthesis to nerve gases (it is a schedule 3B precursor to dimethyl methylphosphonate) (OECD, 2004; OPCW, 2023).

1.3 Detection and quantification

Capillary gas chromatography-flame ionization detection (GC-FID) has been applied to the analysis of dimethyl hydrogen phosphite in aqueous solutions under simulated physiological conditions. The method had a linear calibration curve over a range of 10 to 1000 ng. High-performance liquid chromatography (HPLC) coupled with radioactivity detection was also used to analyse dimethyl hydrogen phosphite

and its degradation products. (Nomeir et al., 1988; IARC, 1990).

More recently, a gas chromatography-mass spectrometry (GC-MS) method was reported for the analysis of dimethyl hydrogen phosphite sprayed over indoor dust particles in a controlled laboratory experiment. The mass spectrometer was operated in selected-ion monitoring (SIM) mode with electron impact ionization (EI) (Favela et al., 2012).

[The Working Group noted that dimethyl hydrogen phosphite has been measured in the air in a flame-retardant manufacturing plant (see Section 1.4.2), but no information was available on the analytical method used.] There were no data available on the use of these or other methods for the detection and quantification of dimethyl hydrogen phosphite in human tissues.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

No data on environmental occurrence were available to the Working Group.

1.4.2 Occupational exposure

Given the fact that dimethyl hydrogen phosphite has been used as a flame retardant on nylon 6 fibres, as a chemical intermediate in the production of pesticides and in lubricant additives and adhesives (IARC, 1990), workers engaged in manufacturing these products are expected to have been exposed. The National Institute for Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NOES) of 1981–1983 estimated that chemical technicians were potentially exposed to dimethyl hydrogen phosphite in the USA [1822 exposed workers were reported; the Working Group estimated a confidence interval of 1184–2460] (NIOSH, 1983).

Data on occupational exposure levels were available from a study published in 1985 (US EPA, 1985). The study in which air monitoring of dimethyl hydrogen phosphite was conducted concerned a manufacturing facility where flame retardants were produced in Charleston, South Carolina, USA. The maximum partial-shift worker exposure was 1.9 ppm [8.6 mg/m^3], and the average exposure was 0.22 ppm [0.99 mg/m^3] (measurement duration, 3–4 hours). For the 8-hour time-weighted average (TWA), these levels were estimated to be 1.1 ppm [4.95 mg/m^3] and 0.16 ppm [0.72 mg/m^3], respectively.

1.4.3 Exposure of the general population

No data on exposure of the general population (including biomonitoring levels) were available to the Working Group.

1.5 Regulations and guidelines

A quantitative limit for exposure to dimethyl hydrogen phosphite occurring in the workplace was found only for Romania (8-hour limit value of 12 mg/m^3) (IFA, 2022a). The United States Environmental Protection Agency (US EPA) has derived acute exposure guideline levels (AEGLs) that are used by emergency planners and responders as guidance in dealing with rare, usually accidental, releases of chemicals into the air (US EPA, 2022a). For dimethyl hydrogen phosphite, interim AEGLs have been available since 2010 (US EPA, 2010) (see Table 1.1).

Because dimethyl hydrogen phosphite can potentially be used in the production of nerve gas, production and export are stringently controlled under the Wassenaar Arrangement, which was signed by 42 countries (Wassenaar Arrangement Secretariat, 2022).

Table 1.1 Acute exposure guideline levels for airborne dimethyl hydrogen phosphite, proposed by the US EPA

Classification	10 minutes	30 minutes	60 minutes	4 hours	8 hours
AEGL-1 Notable discomfort, irritation, or certain asymptomatic non-sensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure	Not recommended[a]	Not recommended[a]	Not recommended[a]	Not recommended[a]	Not recommended[a]
AEGL-2 Irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape	120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)
AEGL-3 Life-threatening health effects or death	190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (280 mg/m^3)

AEGL, acute exposure guideline level; ppm, parts per million; US EPA, United States Environmental Protection Agency.
[a] Not recommended due to insufficient data.
Data from US EPA (2022a).

According to the European Globally Harmonized System Classification and Labelling of Chemicals (GHS), dimethyl hydrogen phosphite is classified as "suspected of causing genetic effects" (H341) and "suspected of causing cancer" (H351) (both in Hazard Category 2) (IFA, 2022b).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

In previous evaluations, the *IARC Monographs* programme concluded that there was *limited evidence* in experimental animals for the carcinogenicity of dimethyl hydrogen phosphite (IARC, 1990, 1999).

Studies of carcinogenicity with dimethyl hydrogen phosphite in experimental animals are summarized in Table 3.1.

3.1 Mouse

In a well-conducted study of chronic toxicity and carcinogenicity that complied with Good Laboratory Practice (GLP), groups of 50 male and 50 female B6C3F$_1$ mice (age, 6–8 weeks) were treated with dimethyl hydrogen phosphite (purity, 97–98%; impurity, 1% trimethyl phosphate) at a dose of 0 (vehicle control-corn oil only), 100, or 200 mg/kg body weight (bw) per day by daily gavage in corn oil (dosing volume, 4.0 mL/kg) 5 days per week for 103 weeks (NTP, 1985; also reported by Dunnick et al., 1986). At study termination, survival was 42/50, 33/50, and 32/50 in males, and 39/50, 37/50, and 34/50 in females, for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. There was a trend for decreased survival in the males ($P = 0.018$, life-table trend test) with the survival rate being significantly lower ($P = 0.029$, life-table test) at the higher dose than in vehicle controls. No differences in survival were observed in treated female mice compared with vehicle controls. Body weights of male mice at the higher dose ranged from 5% to 10% lower than those of mice in the vehicle control group between 28 weeks

Table 3.1 Studies of carcinogenicity in mice and rats exposed to dimethyl hydrogen phosphite

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 6–8 wk 103 wk NTP (1985)	Oral administration (gavage) Purity, 97–98% (impurity, trimethyl phosphate, 1%) Corn oil 0, 100, 200 mg/kg bw 5 days/wk for 103 wk 50, 50, 50 42, 33, 32	No significant increase in tumour incidence in treated animals		*Principal strengths*: GLP study; males and females used; covered most of the lifespan; adequate number of animals per group; high quality of gross descriptions and microscopic examinations; multiple-dose study; appropriate statistics. *Other comments*: male mice at the higher dose had significantly lower survival.
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6–8 wk 103 wk NTP (1985)	Oral administration (gavage) Purity, 97–98% (impurity, trimethyl phosphate, 1%) Corn oil 0, 100, 200 mg/kg bw 5 days/wk for 103 wk 50, 50, 50 39, 37, 34	*Liver* Hepatocellular adenoma		*Principal strengths*: adequate number of animals per group; high quality of gross descriptions and microscopic examinations; multiple-dose study; appropriate statistics; GLP study; males and females used; covered most of the lifespan. *Historical controls*: hepatocellular adenoma: laboratory, 4/148 (2.7% ± 2.4%; range, 0–4%); NTP studies, 47/1176 (4.0% ± 2.6%; range, 0–10%); hepatocellular adenoma or carcinoma (combined): laboratory, 7/148 (4.7% ± 3.0%; range, 2–8%); NTP studies, 80/1176 (6.8% ± 3.4%; range, 2–14%).
		0/50, 6/49* (12%), 3/50 (6%)	*P = 0.016, incidental tumour and life-table tests; P = 0.012, Fisher exact test NS, Cochran–Armitage trend test, incidental tumour and life-table trend tests	
		Hepatocellular carcinoma		
		2/50, 0/49, 0/50	NS	
		Hepatocellular adenoma or carcinoma (combined)		
		2/50, 6/49, 3/50	NS	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 7 wk 103 wk NTP (1985)	Oral administration (gavage) Purity, 97–98% (impurity, trimethyl phosphate, 1%) Corn oil 0, 100, 200 mg/kg bw 5 days/wk for 103 wk 50, 50, 50 39, 29, 23	*Lung* Bronchioloalveolar adenoma		*Principal strengths*: GLP study; males and females used; covered most of the lifespan; adequate number of animals per group; multiple-dose study; high quality of gross descriptions and microscopic examinations; appropriate statistics. *Other comments*: male rats at the higher dose had significantly lower survival. *Historical controls*: lung bronchioloalveolar adenoma: laboratory, 2/150 (1.3% ± 1.2%; range, 0–2%); NTP studies, 34/1143 (3.0% ± 1.9%; range, 0–6%); lung bronchioloalveolar carcinoma: laboratory, 3/150 (2.0% ± 0.0%; range, NR); NTP studies, 16/1143 (1.4% ± 1.5%; range, 0–6%); lung bronchioloalveolar adenoma or carcinoma (combined): laboratory, 5/150 (3.3% ± 1.2%; range, 2–4%); NTP studies, 50/1143 (4.4% ± 2.4%; range, 0–8%); lung squamous cell carcinoma: laboratory, 0%; NTP studies, 2/1143 (0.2% ± 0.58%; range, 0–2%); forestomach squamous cell papilloma: laboratory, 0/147; NTP studies, 2/1114 (0.002%) [range, NR]; forestomach squamous cell carcinoma: laboratory, 0/147, NTP studies, 0/1114 [range, NR]; forestomach squamous cell papilloma or carcinoma (combined): laboratory, 0/147; NTP studies, 2/1114 (0.002%) [range, NR].
		0/50, 0/50, 5/50*	$P = 0.004$, life-table trend test; $P = 0.017$, incidental tumour trend test; $P = 0.006$, Cochran–Armitage trend test *$P = 0.018$, life-table test; *$P = 0.028$, Fisher exact test; NS, incidental tumour test	
		Bronchioloalveolar carcinoma		
		0/50, 1/50, 20/50*	$P < 0.001$, life-table trend test; $P < 0.001$, incidental tumour trend test; $P < 0.001$, Cochran–Armitage trend test *$P < 0.001$, life-table test; *$P < 0.001$, incidental tumour test; *$P < 0.001$, Fisher exact test	
		Bronchioloalveolar adenoma or carcinoma (combined)		
		0/50, 1/50, 24/50*	$P < 0.001$, life-table trend test, $P < 0.001$, incidental tumour trend test; $P < 0.001$, Cochran–Armitage trend test *$P < 0.001$, life-table test; *$P < 0.001$, incidental tumour test; *$P < 0.001$, Fisher exact test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 7 wk 103 wk NTP (1985) (cont.)		Squamous cell carcinoma		
		0/50, 0/50, 5/50*	*P* = 0.004, life-table trend test; *P* = 0.034, incidental tumour trend test; *P* = 0.006, Cochran–Armitage trend test **P* = 0.020, life-table test; **P* = 0.028, Fisher exact test; NS, incidental tumour test	
		Forestomach		
		Squamous cell papilloma		
		0/50, 1/50 (2%), 3/50 (6%)	*P* = 0.032, life-table trend test; *P* = 0.052, incidental tumour trend test; *P* = 0.037, Cochran–Armitage trend test NS, life-table test, incidental tumour test, Fisher exact test	
		Squamous cell carcinoma		
		0/50, 0/50, 3/50 (6%)	*P* = 0.023, life-table trend test; NS, incidental tumour trend test; *P* = 0.037, Cochran–Armitage trend test NS, life-table test, incidental tumour test, Fisher exact test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 7 wk 103 wk NTP (1985) (cont.)		Squamous cell papilloma or carcinoma (combined)		
		0/50, 1/50, 6/50*	P = 0.002, life-table trend test; P = 0.006, incidental tumour trend test; P = 0.005, Cochran–Armitage trend test *P = 0.006, life-table test; *P = 0.025, incidental tumour test; *P = 0.013, Fisher exact test	
Full carcinogenicity Rat, F344/N (F) 7 wk 103 wk NTP (1985)	Oral administration (gavage) Purity, 97–98% (impurity, trimethyl phosphate, 1%) Corn oil 0, 50, 100 mg/kg bw 5 days/wk for 103 wk 50, 50, 50 40, 33, 32	*Lung* Bronchioloalveolar carcinoma		*Principal strengths*: GLP study, studies in both males and females, covers most of the lifespan, adequate number of animals per group, multiple dose study, high quality of gross descriptions and microscopic examinations, appropriate statistics. *Historical controls*: lung bronchioloalveolar carcinoma: laboratory, 1/150 (0.7% ± 1.2%; range, 0–2%); NTP studies, 10/1142 (0.9% ± 1.3%; range, 0–4.2%); forestomach squamous cell papilloma or carcinoma (combined): NR.
		0/50, 1/49, 3/50 (6%)	P = 0.047, life-table and incidental tumour trend tests; NS, Cochran–Armitage trend test NS, life-table test, incidental tumour test, Fisher exact test	
		Forestomach Squamous cell papilloma		
		0/50, 0/50, 1/48	[NS]	
		Squamous cell carcinoma		
		0/50, 0/50, 1/48	[NS]	
		Squamous cell papilloma or carcinoma (combined)		
		0/50, 0/50, 2/48	[NS]	

bw, body weight; F, female; GLP, Good Laboratory Practice; M, male; NR, not reported; NS, not significant; NTP, National Toxicology Program; wk, week(s).

and study termination. Body weights of treated females were similar to those of mice in the vehicle control group throughout the study. The results of histopathological examination were reported for all major tissues and gross lesions.

In female mice, the incidence of hepatocellular adenoma was 0/50, 6/49 (12%), and 3/50 (6%) for the groups for the groups at 0 (control), 100, and 200 mg/kg bw, respectively, and was significantly increased ($P = 0.012$, Fisher exact test; $P = 0.016$, life-table test; $P = 0.016$, incidental tumour test) in the group at the lower dose, exceeding the upper bound of the range observed in historical controls from this laboratory – 4/148 (2.7 ± 2.4%); range, 0–4.0% – and from National Toxicology Program (NTP) studies – 47/1176 (4.0 ± 2.6%); range, 0–10%. The incidence of hepatocellular adenoma or carcinoma (combined) was 2/50 (4%), 6/49 (12%), and 3/50 (6%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. At the lower dose, the incidence exceeded the upper bound of the range observed in historical controls from this laboratory – 7/148 (4.7 ± 3.0%); range, 2–8% – but not from the concurrent NTP studies – 80/1176 (6.8 ± 3.4%); range, 2–14%. [The Working Group noted that hepatocellular carcinoma was observed in two animals in the control group and in none of the treated animals.] In male mice, there were no significant treatment-related effects on the incidence of any tumour.

For both male and female mice, there were no increases in the incidence of non-neoplastic lesions at sites at which tumour incidence was considered to be increased.

[The Working Group noted that this was a well-conducted study that complied with GLP, both sexes were used, the duration of exposure and observation was adequate, an adequate number of animals per group was used, and the descriptions of gross and microscopic examinations were of high quality. The Working Group noted that the impurity trimethyl phosphate had been reported to show clear evidence of carcinogenicity in male Fischer 344 rats (NCI, 1978). However, the Working Group considered that the presence of 1% trimethyl phosphate did not significantly contribute to the results of the present study.]

3.2 Rat

In a well-conducted study of chronic toxicity and carcinogenicity that complied with GLP, groups of 50 male and 50 female F344/N rats (age, about 7 weeks) were treated by gavage with dimethyl hydrogen phosphite (purity, 97–98%; impurity, 1% trimethyl phosphate; mixed in corn oil). Male rats were given doses of 0 (vehicle control, corn oil only), 100, or 200 mg/kg bw per day (dosing volume, 4.0 mL/kg), 5 days per week for 103 weeks (NTP, 1985; also reported by Dunnick et al., 1986). Female rats were given doses of 0 (vehicle control, corn oil only), 50, or 100 mg/kg bw per day under similar conditions. At study termination, survival was 39/50, 29/50, and 23/50 in males, and 40/50, 33/50, and 32/50 in females, in the control group and groups at the lower and higher dose, respectively; the survival in males at the higher dose was significantly lower ($P = 0.008$, life-table test) than that in vehicle controls, and there was a significant trend observed ($P = 0.009$, life-table trend test). Decreased survival in treated male rats was considered to be attributable to an increase in the incidence of chronic interstitial pneumonia. In treated females, survival was not significantly affected. Mean body weights of male rats at the higher dose were observed to be 10–15% lower than those of the vehicle controls from 24 weeks to the end of the study. Mean body weights of male rats at the lower dose and female rats at the lower and higher dose were similar to those of the vehicle controls. The results of histopathological examination were reported for all major tissues and gross lesions.

In male rats, there was a significant positive trend ($P = 0.004$, life-table trend test; $P = 0.017$, incidental tumour trend test; $P = 0.006$, Cochran–Armitage trend test) in the incidence of bronchioloalveolar adenoma: 0/50, 0/50, and 5/50 (10%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of bronchioloalveolar adenoma was significantly increased at the higher dose ($P = 0.018$, life-table test; $P = 0.028$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls from this laboratory – 2/150 (1.3 ± 1.2%); range, 0–2% – and from NTP studies – 34/1143 (3.0 ± 1.9%); range, 0–6%. There was a significant positive trend ($P < 0.001$, life-table trend test; $P < 0.001$, incidental tumour trend test; $P < 0.001$, Cochran–Armitage trend test) in the incidence of bronchioloalveolar carcinoma: 0/50, 1/50 (2%), and 20/50 (40%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of bronchioloalveolar carcinoma was significantly increased at the higher dose ($P < 0.001$, life-table test; $P < 0.001$, incidental tumour test; $P < 0.001$, Fisher exact test) and exceeded the incidence observed in historical controls from this laboratory – 3/150 (2 ± 0%); range, not reported – and from NTP studies – 16/1143 (1.4 ± 1.5%); range, 0–6%. There was a significant positive trend ($P < 0.001$, life-table trend test; $P < 0.001$, incidental tumour trend test; $P < 0.001$, Cochran–Armitage trend test) in the incidence of bronchioloalveolar adenoma or carcinoma (combined): 0/50, 1/50 (2%), and 24/50 (48%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of bronchioloalveolar adenoma or carcinoma (combined) was significantly increased at the higher dose ($P < 0.001$, life-table test; $P < 0.001$, incidental tumour test; $P < 0.001$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls from this laboratory – 5/150 (3.3 ± 1.2%); range, 2–4% – and from NTP studies – 50/1143 (4.4 ± 2.4%); range, 0–8%. There was a significant positive trend ($P = 0.004$, life-table trend test; $P = 0.034$, incidental tumour trend test; $P = 0.006$, Cochran–Armitage trend test) in the incidence of squamous cell carcinoma of the lung: 0/50, 0/50, and 5/50 (10%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of squamous cell carcinoma of the lung was significantly increased at the higher dose ($P = 0.020$, life-table test; $P = 0.028$, Fisher exact test) and exceeded the upper bound of the range observed in historical controls from this laboratory (0%) and from NTP studies – 2/1143 (0.2 ± 0.58%); range, 0–2%. There was a significant positive trend ($P = 0.032$, life-table trend test; $P = 0.052$, incidental tumour trend test; $P = 0.037$, Cochran–Armitage trend test) in the incidence of squamous cell papilloma of the forestomach: 0/50, 1/50 (2%), and 3/50 (6%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of squamous cell papilloma of the forestomach in the groups at the lower and higher dose exceeded the incidence in historical controls from this laboratory (0/147) and from NTP studies – 2/1114 (0.002%). There was a significant positive trend ($P = 0.023$, life-table trend test; $P = 0.037$, Cochran–Armitage trend test) in the incidence of squamous cell carcinoma of the forestomach: 0/50, 0/50, and 3/50 (6%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence in the group at the higher dose exceeded the incidence in historical controls from this laboratory (0/147) and from NTP studies (0/1114). There was a significant positive trend ($P = 0.002$, life-table trend test; $P = 0.006$, incidental tumour trend test; $P = 0.005$, Cochran–Armitage trend test) in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach: 0/50, 1/50 (2%), and 6/50 (12%) for the groups at 0 (control), 100, and 200 mg/kg bw, respectively. The incidence of squamous cell papilloma or carcinoma (combined) of the forestomach was significantly increased at the higher dose ($P = 0.006$, life-table test; $P = 0.025$, incidental tumour test; $P = 0.013$, Fisher exact test). The incidence in the groups at

the lower and higher dose exceeded the incidence in historical controls from this laboratory (0/147) and from NTP studies – 2/1114 (0.002%).

In female rats, there was a significant positive trend (*P* = 0.047, life-table trend test; *P* = 0.047, incidental tumour trend test) in the incidence of bronchioloalveolar carcinoma: 0/50, 1/49 (2%), 3/50 (6%) for the groups at 0 (control), 50, and 100 mg/kg bw, respectively. The incidence in the group at the higher dose exceeded the upper bound of the range observed in historical controls from this laboratory – 1/150 (0.7 ± 1.15%); range, 0–2% – and from NTP studies – 10/1142 (0.9 ± 1.34%); range, 0–4%.

Regarding non-neoplastic lesions, the incidence of lesions of the lung and forestomach was considered to be treatment-related in males and females. In the lung, the incidence of alveolar epithelial hyperplasia, adenomatous hyperplasia, and chronic interstitial pneumonia was significantly increased in male and female rats at the higher dose. The incidence of squamous metaplasia of the lung was also increased in male rats at the higher dose. In the forestomach, the incidence of hyperplasia and hyperkeratosis was significantly increased in males at the higher dose. The incidence of forestomach hyperplasia was also significantly increased in females at the higher dose. [The Working Group noted that this was a well-conducted study that complied with GLP, both sexes were used, the duration of exposure and observation was adequate, there was an adequate number of animals per group, and the descriptions of gross and microscopic examinations were of high quality. The Working Group noted that the impurity trimethyl phosphate had been reported to show clear evidence of carcinogenicity in male F344 rats (NCI, 1978). However, the Working Group considered that the presence of 1% trimethyl phosphate did not significantly contribute to the results of the present study.]

3.3 Evidence synthesis for cancer in experimental animals

The carcinogenicity of dimethyl hydrogen phosphite has been assessed in one well-conducted study that complied with GLP in male and female B6C3F$_1$ mice (NTP, 1985; also reported by Dunnick et al., 1986), and in one well-conducted GLP study in male and female F344/N rats (NTP, 1985; also reported by Dunnick et al., 1986) treated by oral administration (gavage).

In the GLP study in male and female B6C3F$_1$ mice treated by gavage (NTP, 1985; also reported by Dunnick et al., 1986), there was a significant increase in the incidence of hepatocellular adenoma in females at the lower dose. In male mice, there were no significant treatment-related effects on the incidence of any tumour.

In the GLP study in male and female F344/N rats treated by gavage (NTP, 1985; also reported by Dunnick et al., 1986), there was a significant positive trend in the incidence of bronchioloalveolar carcinoma, and incidence was significantly increased at the higher dose. There was a significant positive trend in the incidence of bronchioloalveolar adenoma in males, and incidence was significantly increased at the higher dose. There was a significant positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined), and incidence was significantly increased at the higher dose. There was a significant positive trend in the incidence of squamous cell carcinoma of the lung, and incidence was significantly increased at the higher dose. There was a significant positive trend in the incidence of squamous cell papilloma of the forestomach and a significant positive trend in the incidence of squamous cell carcinoma of the forestomach. There was a significant positive trend in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach, and incidence was significantly increased at the higher dose. In female rats, there was a significant positive

trend in the incidence of bronchioloalveolar carcinoma.

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Data on the absorption, distribution, metabolism, and excretion of dimethyl hydrogen phosphite in humans were not available to the Working Group.

4.1.2 Experimental systems

The scientific literature on the absorption, distribution, metabolism, and excretion of dimethyl hydrogen phosphite was limited to one study conducted by the NTP (NTP, 1985; Nomeir & Matthews, 1997). This study consisted of in vivo and in vitro experimental components. Distribution and metabolism data were obtained using radioactivity measurements. Male F344/N rats and male B6C3F$_1$ mice were treated by gastric intubation with [^{14}C]-labelled dimethyl hydrogen phosphite (in corn oil; volume, 4 mL/kg bw) at a dose ranging from 10 to 200 mg/kg bw. Dimethyl hydrogen phosphite was readily and almost entirely (approximately 98%) absorbed in the gastrointestinal tract in both rats and mice, and widely distributed in the tissues of both rodent species. In the rats, 24 hours after administration of a dose of 10, 100, or 200 mg/kg bw, the liver and kidneys contained the highest levels of [^{14}C]-labelled dimethyl hydrogen phosphite equivalents (liver, 8.5 ± 1.0 to 165.0 ± 25.0 µg/g wet tissue; kidney, 6.8 ± 1.3 to 175 ± 40.0 µg/g wet tissue), followed by the forestomach, spleen, small intestine, and lung. The lowest concentrations of [^{14}C]dimethyl hydrogen phosphite equivalents were found in the brain, adipose tissue, muscle, and testes (range, 1.2–25 µg/g wet tissue). The concentrations of dimethyl hydrogen phosphite in tissues were approximately proportional to the administered dose. The pattern of distribution at later time points (2, 5, and 10 days) after administration of a single dose at 200 mg/kg bw was similar to that observed at 24 hours. The rate of clearance at these later time points was markedly decreased compared with that at 24 hours. Concentrations of dimethyl hydrogen phosphite in all tissues increased with the number of daily doses at 200 mg/kg bw (one, two, and five) administered.

The tissue distribution pattern for dimethyl hydrogen phosphite in male mice at 1, 2, and 5 days after administration of a single dose at 200 mg/kg bw was similar to that observed in male rats. Tissue concentrations were substantially lower in mice than in rats. The metabolism of dimethyl hydrogen phosphite in vivo was analysed in urine samples by high-performance liquid chromatography. In rats and mice and at all doses administered, dimethyl hydrogen phosphite was metabolized to monomethyl hydrogen phosphite, which was excreted in the urine. The single methyl group removed during the metabolism of dimethyl hydrogen phosphite to monomethyl hydrogen phosphite was further oxidized to carbon dioxide (CO_2), which was released in the expired air.

The in vitro metabolism of dimethyl hydrogen phosphite was investigated using microsomal fractions from the liver, lung, kidney, forestomach, and glandular stomach of the treated rats. Dimethyl hydrogen phosphite was metabolized to formaldehyde in a concentration-dependent manner. This reaction required the presence of NADPH (nicotinamide adenine dinucleotide phosphate, reduced form). Microsomes from the liver, lung, and kidney all demonstrated a similar level of metabolic activity, which was higher than that of microsomes from the forestomach and glandular stomach. [The Working Group noted that metabolism to formaldehyde

in vivo was not reported in this study, although this was imputed on the basis of the results with microsomal fractions in vitro.] Excretion of dimethyl hydrogen phosphite was rapid in both rats and mice, with most being released within the first 24 hours after dose administration. At the doses studied (10, 100, and 200 mg/kg bw) in rats, most of the [^{14}C]dimethyl hydrogen phosphite-related radiolabel was excreted as CO_2 in expired air (49–57%) and as monomethyl hydrogen phosphite in the urine (28–38%), with faeces containing only 2%. After dosing, elimination continued in expired air for approximately 12 hours and in the urine for up to 24 hours. The dose level did not affect the rate or route of elimination. Repeated administration of a 200 mg/kg bw dose daily for 5 days had little effect on metabolism to CO_2 or elimination in the urine.

In mice treated with dimethyl hydrogen phosphite at a dose of 200 mg/kg bw, 49% was excreted in the urine, 44% as CO_2 in expired air, 2.5% as organic volatiles, and 1–2% in the faeces.

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether dimethyl hydrogen phosphite is genotoxic. Sparse data, mostly derived from the NTP report (NTP, 1985), were also available on whether dimethyl hydrogen phosphite induces oxidative stress; induces chronic inflammation; or alters cell proliferation, cell death, or nutrient supply. No data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 *Is genotoxic*

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.1.

Male B6C3F$_1$ mice were injected intraperitoneally on three consecutive days with dimethyl hydrogen phosphite at a dose of 250 or 500 mg/kg bw (Shelby et al., 1993). Bone marrow smears were prepared 24 hours after the third treatment and used for the micronucleus test assay. An initial test showed a significant ($P < 0.001$, ANOVA trend test) increase in the frequency of micronucleated polychromatic erythrocytes per 1000 polychromatic erythrocytes scored at 500 mg/kg bw (6.1) compared with controls (2.1). The repeat test did not show a significant ($P = 0.078$, ANOVA trend test) increase (the frequency of micronucleated polychromatic erythrocytes was 2.7 in controls versus 4.2 at the higher dose). [The Working Group noted that although a reproducible, statistically significant trend was not seen between the two tests, the study results were deemed to show adequate evidence of an effect. It was also noted that a re-evaluation of these data, reported in the NTP database Chemical Effects in Biological Systems (CEBS), indicated significance ($P < 0.001$, one-tailed Pearson chi-squared test) by the pairwise test (NTP, 2018).]

(ii) Non-human mammalian cells in vitro

See Table 4.2.

McGregor et al. (1988) tested the mutagenic potential of dimethyl hydrogen phosphite in the forward mutation assay in L5178Y *Tk*$^{+/-}$ mouse lymphoma cells. Cells (6×10^6 per culture; two cultures per concentration) were exposed to dimethyl hydrogen phosphite at five concentrations for 4 hours, with and without metabolic activation (post-mitochondrial 9000 × *g* supernatant fractions of liver homogenates, S9), and then cultured for 2 days before testing. In the presence of S9, dimethyl hydrogen phosphite was assessed at concentrations up to 2500 μg/mL;

Table 4.1 Genetic and related effects of dimethyl hydrogen phosphite in non-human mammals in vivo

End-point	Assay	Species, strain (sex)	Tissue	Results[a]	Dose (LOED or HID)	Route, duration, dosing regimen	Reference
Micronucleus formation	Micronucleus assay	Mouse, B6C3F$_1$ (M)	Bone marrow (smears)	+ –	500 mg/kg bw, 1st test 500 mg/kg bw, 2nd test	Intraperitoneally; 250 and 500 mg/kg bw for 3 days.	Shelby et al. (1993)

bw, body weight; HID, highest ineffective dose; LOED, lowest observed effective dose; M, male.
[a] +, positive; –, negative.

Table 4.2 Genetic and related effects of dimethyl hydrogen phosphite in non-human mammalian cells in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Gene mutation (forward mutations)	Mouse, L5178Y *Tk*$^{+/-}$ lymphoma cells	–	+	2100 mg/mL	Five-concentration range up to 2200 mg/mL (–S9), for 4 hours. Five-concentration range up to 2500 mg/mL (+S9), for 4 hours. Decreases in pH observed.	McGregor et al. (1988)
Chromosomal aberrations	Hamster, Chinese, ovary cells (CHO)	+	+	250 µg/mL	Concentration range, 0.0–5000 µg/mL. Chromosome fusion at the highest dose.	Gulati et al. (1989)
Sister-chromatid exchange	Hamster, Chinese, ovary cells (CHO)	+	+	1600 µg/mL	Concentration range, 0.0–4000 µg/mL.	Gulati et al. (1989)
Unscheduled DNA synthesis	Rat, F344, Aroclor-pretreated adult males, primary hepatocytes Rat, F344, 3-MC-pretreated adult males, primary hepatocytes	+ +	NA NA	0.01 µL/mL 0.025 µL/mL	Treatment concentrations, 0.01–5.0 µL/mL. Cytotoxicity was observed at the highest concentration in Aroclor-pretreated hepatocytes and at the three highest concentrations in 3-MC-pretreated hepatocytes.	Shaddock et al. (1990)

CHO, Chinese hamster ovary; HIC, highest ineffective concentration; LEC, lowest effective concentration; 3-MC, 3-methylcholanthrene; NA, not applicable; S9, 9000 × *g* supernatant.
[a] +, positive; –, negative.

a significant response was obtained with the lowest observed effective concentration (LOEC) of 2100 µg/mL. In the absence of S9, dimethyl hydrogen phosphite was tested at up to 2200 µg/mL because of poor growth during the expression period. No significant mutagenic response was observed at any concentration in the absence of metabolic activation. [The Working Group noted that the requirement for S9 in order to obtain a significant response suggested that dimethyl hydrogen phosphite needed to be metabolically activated to induce mutagenicity. The Working Group also noted that dimethyl hydrogen phosphite caused reductions in pH levels in the culture medium either in the presence or absence of S9. However, it was concluded that, in this study, the reduction of pH did not alter the mutagenic effect of dimethyl hydrogen phosphite.]

Dimethyl hydrogen phosphite was tested for induction of sister-chromatid exchange (concentration range, 0.0–4000 µg/mL) and chromosomal aberration (concentration range, 0.0–5000 µg/mL) in Chinese hamster ovary cells (Gulati et al., 1989). Sister-chromatid exchange and chromosomal aberration were induced in both the presence and absence of S9. Sister-chromatid exchange was observed at concentrations of 250–4000 µg/mL and chromosomal aberration at 1600–5000 µg/mL. In most cells treated with dimethyl hydrogen phosphite at 5000 µg/mL, all 21 chromosomes were fused together.

A study using primary hepatocyte cultures derived from livers of adult male Fischer 344 rats pretreated with hepatic mixed-function oxidase inducers, Aroclor and 3-methylcholanthrene, showed that dimethyl hydrogen phosphite induced a significant increase in unscheduled DNA synthesis in rats pretreated with Aroclor (0.01–2.5 µL/mL) or with 3-methylcholanthrene (0.025–0.250 µL/mL) (Shaddock et al., 1990).

(c) Non-mammalian systems

See Table 4.3.

Dimethyl hydrogen phosphite was not mutagenic in the *Salmonella typhimurium* assay system when tested in strains TA98, TA100, TA1535, and TA1537 at 100–10 000 µg/plate, with or without metabolic activation with S9 from livers of Aroclor 1254-induced Sprague-Dawley rats or Syrian hamsters.

When administered via feeding (650 ppm) or injection (1500 ppm), dimethyl hydrogen phosphite did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (NTP, 1985).

Woodruff et al. (1985) tested the ability of dimethyl hydrogen phosphite to induce sex-linked recessive lethal mutations in *D. melanogaster* generations after mating 24-hour-old Canton-S males fed with dimethyl hydrogen phosphite (650 ppm) for 3 days, or 72-hour-old (adult) males treated by injection (1500 ppm). Both routes of exposure gave negative results.

4.2.2 Induces oxidative stress

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

Daily treatment with dimethyl hydrogen phosphite (200 mg/kg bw, via gavage) of male Fischer 344 rats for 4, 5, or 6 weeks showed no effect on the activities of superoxide dismutase or glutathione *S*-transferase in the soluble fraction of the liver, lung, kidney, forestomach, or glandular stomach (Nomeir & Uraih 1988).

4.2.3 Induces chronic inflammation

(a) Humans

No data were available to the Working Group.

Table 4.3 Genetic and related effects of dimethyl hydrogen phosphite in non-mammalian experimental systems

Test system (species, strain)	Assay	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Drosophila melanogaster	Sex-linked recessive lethal test	Recessive lethal mutations	– –	NA NA	650 ppm by feeding 1500 ppm by injection		NTP (1985)
Drosophila melanogaster	Sex-linked recessive lethal test	Sex-linked recessive lethal mutations	– –	NA NA	650 ppm by feeding 1500 ppm by injection		Woodruff et al. (1985)
Salmonella typhimurium	Ames bacterial reverse mutation test	Gene mutation			100–10 000 µg/plate	Cytotoxicity observed at the highest concentration.	NTP (1985)
TA98 (frameshift +1)			–	–S9 (rat); –S9 (hamster)			
TA98, TA1538 (frameshift +1)			–	–S9 (rat); –S9 (hamster)			
TA1535 (base substitution, at GC)			–	–S9 (rat); –S9 (hamster)			
TA100 (base substitution, at GC)			–	–S9 (rat); –S9 (hamster)			
TA1537 (frameshift –1)			–	–S9 (rat); –S9 (hamster)			

HIC, highest ineffective concentration; LEC, lowest effective concentration, NA, not applicable; ppm, parts per million; S9, 9000 × *g* supernatant.

[a] –, negative.

(b) Experimental systems

(i) Non-human mammals in vivo

Subepithelial inflammation with minimal infiltrate in the submucosa and occasional submucosal intercellular and intracellular oedema were observed in the forestomach of male Fischer 344 rats treated daily with dimethyl hydrogen phosphite (200 mg/kg bw, by gavage) for 6 weeks. No gross changes were observed in the lung or forestomach of rats during necropsy or in the lung during microscopic examination (Nomeir & Uraih, 1988).

In a study conducted by the NTP, male and female F344/N rats were treated by gavage with dimethyl hydrogen phosphite at doses of 0, 50, 100, or 200 mg/kg bw (for males), or 0, 50, and 100 mg/kg bw (for females), 5 days per week for 103 weeks. An increased incidence of chronic inflammation, in the form of chronic interstitial pneumonia, was observed in the treated male rats (both at 100 and 200 mg/kg bw) and in females at the highest dose. No increased incidence of inflammation was observed in either male or female B6C3F$_1$ mice that were treated with dimethyl hydrogen phosphite according to the same protocol as for the male rats (NTP, 1985).

4.2.4 Alters cell proliferation, cell death, or nutrient supply

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

In male Fischer 344 rats treated daily by gavage with dimethyl hydrogen phosphite (200 mg/kg bw) for 6 weeks, histological examination of the forestomach identified lesions characterized by epithelial hyperplasia and hyperkeratosis (Nomeir & Uraih, 1988).

Dimethyl hydrogen phosphite was administered via gavage, 5 days per week for 103 weeks, to male (0, 100, or 200 mg/kg bw) and female (0, 50, 100 mg/kg bw) F344/N rats, and to male and female B6C3F$_1$ mice (0, 100, or 200 mg/kg bw). Male rats showed an increased incidence of hyperplasia and squamous metaplasia (highest dose only) in the lung and hyperplasia and hyperkeratosis in the forestomach. Female rats at the highest dose showed an increased incidence of adenomatous hyperplasia and alveolar epithelium hyperplasia in the lung and an increased incidence of forestomach hyperplasia. Dimethyl hydrogen phosphite caused hyperplasia and hyperkeratosis in the forestomach of male rats. No increased incidence of hyperplasia or metaplasia was observed in male or female mice (NTP, 1985).

4.3 Other relevant evidence

Significant increases (> 60% above control values) in levels of nonprotein soluble sulfhydryls were observed in the forestomach of male Fischer 344 rats treated with dimethyl hydrogen phosphite via gavage at a daily dose of 200 mg/kg bw for 6 weeks or with a single intravenous or oral dose of 1000 mg/kg bw, suggesting that dimethyl hydrogen phosphite interferes with sulfhydryl metabolism. [The Working Group noted that the increase in sulfhydryl levels could be a possible contributing factor to the development of lesions in these tissues after long-term exposure to dimethyl hydrogen phosphite.] The activity of soluble carboxylesterase was significantly reduced in the lung and forestomach of rats treated with dimethyl hydrogen phosphite (200 mg/kg bw per day for 6 weeks) (Nomeir & Uraih 1988), which could possibly make these tissues susceptible to further chemical exposures as this enzyme is involved in the hydrolytic detoxification of many toxic chemicals. A significant increase in levels of serum angiotensin-converting enzyme was also observed in rats exposed to dimethyl hydrogen phosphite at 200 mg/kg bw

per day for 4, 5, or 6 weeks, suggesting early lung injury in these animals (Nomeir & Uraih 1988).

4.4 Evaluation of high-throughput in vitro toxicity screening data

Dimethyl hydrogen phosphite was tested in high-throughput toxicity screening assays under the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al., 2019). Chemical samples were procured at high purity, prepared in dimethyl sulfoxide stock solutions at a concentration of about 20 mM, and tested over a period of several years in biochemical and cellular bioassays measuring a wide variety of biological end-points. In addition, chemical analysis of the samples was done in high-throughput fashion at an early and a late stage of the sample testing lifetime for these samples, as described in Tice et al. (2013).

Data on testing results from the concentration–response testing design for all end-points were analysed for significant activity and an active/inactive "hit call" was made for each response, together with a potency value (Filer et al., 2017). For all active calls, individual concentration–response curves were examined to ensure that biologically meaningful activity was detected. Bioassay end-points were mapped, where possible, to the key characteristics of carcinogens using the "kc-hits" software (key characteristics of carcinogens – high-throughput screening discovery tool, available from https://gitlab.com/i1650/kc-hits; Reisfeld et al., 2022) to aid in providing mechanistic insights (Chiu et al., 2018). The detailed results are available in the supplementary material for this volume (Annex 2, Supplementary material for Section 4, Evaluation of high-throughput in vitro toxicity screening data, online only, available from: https://publications.iarc.who.int/631) and are briefly summarized below.

The results for dimethyl hydrogen phosphite high-throughput toxicity testing in the CompTox Chemicals Dashboard encompassed 440 assay end-points, of which 191 were mapped to the key characteristics of carcinogens. [The Working Group noted that in the ToxCast database an alternative name of the agent, dimethyl phosphonate, was used.] The cytotoxicity limit was estimated to be > 1 mM (US EPA, 2022b). Dimethyl hydrogen phosphite was inactive in all except seven of the mapped assay end-points, including three with curve-fitting warning flags. All seven of the positive hit calls were mapped to key characteristic 8 (KC8), "modulates receptor-mediated effects", and six of these measured signalling in the estrogen receptor pathway. Four of the six did not have warning flags, and half-maximal activity concentrations (AC_{50}s) ranged from 8.3 to 22.2 µM. However, 11 other assay end-points measuring estrogen-receptor signalling showed negative hit calls. The other assay with a positive hit call for KC8 was for antagonism of the progesterone receptor but with a flag for activity detected only at the highest concentration tested (89 µM). [The Working Group considered this to be very weak evidence of modulation of receptor-mediated effects.]

The results of chemical analysis of the stock solutions for dimethyl hydrogen phosphite (available from the Tox21 Samples database) were inconsistent (NIH, 2022). Two testing samples were analysed: Tox21_201901 and Tox21_302799. Tox21_201901 was reported to have a purity of < 50% on initial analysis and "unknown or inconclusive" on analysis 4 months later. The second sample, Tox21_302799, gave an incorrect molecular weight on initial analysis, but dimethyl hydrogen phosphite was detected with a purity > 90% on the later analysis. [The Working Group considered the testing results for dimethyl hydrogen phosphite to be of low confidence, without the ability to link specific samples to bioactivity testing.]

5. Summary of Data Reported

5.1 Exposure characterization

Dimethyl hydrogen phosphite is a High Production Volume chemical that is used as an intermediate in the manufacture of adhesives, lubricants, organophosphate pesticides (e.g. glyphosate), and pharmaceuticals (α-aminophosphonates). It is also used as a stabilizer in oil and plaster, and as a steel corrosion inhibitor. Dimethyl hydrogen phosphite is used as a reactive flame retardant in textile finishing, cellulosic textiles, acrolein-grafted polyamide fibres and polyethylene. The production and export of dimethyl hydrogen phosphite is stringently controlled under the Wassenaar Arrangement on Export Controls for Conventional Arms and Dual-Use Goods and Technologies because it can be converted by chemical synthesis to nerve gases.

The most relevant occupational exposure route to dimethyl hydrogen phosphite is respiratory. Exposure data were only available for its use in the production of flame retardants. There were no available data on environmental occurrence nor on exposure of the general population.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Treatment with dimethyl hydrogen phosphite caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in both sexes of a single species (rat) in a well-conducted study that complied with Good Laboratory Practice.

Dimethyl hydrogen phosphite was administered orally (by gavage) to male and female F344/N rats in one study that complied with Good Laboratory Practice. In males, dimethyl hydrogen phosphite caused an increase in the incidence of bronchioloalveolar carcinoma of the lung, bronchioloalveolar adenoma or carcinoma (combined) of the lung, squamous cell carcinoma of the lung, forestomach squamous cell carcinoma, and forestomach squamous cell papilloma or carcinoma (combined). In females, dimethyl hydrogen phosphite caused an increase in the incidence of bronchioloalveolar carcinoma of the lung.

5.4 Mechanistic evidence

No data were available on the absorption, distribution, metabolism, and excretion of dimethyl hydrogen phosphite in humans. Dimethyl hydrogen phosphite was absorbed in the gastrointestinal tract of both mice and rats. Distribution was over a wide and similar range of tissues in mice and rats, with tissue concentrations being substantially lower in mice. In both rats and mice, dimethyl hydrogen phosphite was metabolized either to monomethyl hydrogen phosphite and excreted in the urine or to CO_2 and released in expired air. Dimethyl hydrogen phosphite was metabolized to formaldehyde in vitro, but no evidence was available for metabolism in vivo. Dimethyl hydrogen phosphite was excreted in the urine, expired air, and faeces, or as organic volatiles (mice only).

There was no mechanistic evidence available for dimethyl hydrogen phosphite regarding the key characteristics of carcinogens in exposed humans or in human primary cells or tissues.

Overall, the mechanistic evidence regarding the key characteristic of carcinogens "is genotoxic" is suggestive but inconsistent across different experimental systems. Dimethyl hydrogen phosphite induced a mutagenic response in two different experiments in mouse lymphoma cells

only in the presence of metabolic activation. One study using Chinese hamster ovary cells showed that dimethyl hydrogen phosphite induced sister-chromatid exchange and chromosomal aberration in the presence and absence of metabolic activation. Dimethyl hydrogen phosphite was not mutagenic in several *Salmonella typhimurium* strains in the presence and absence of metabolic activation. Dimethyl hydrogen phosphite did not induce sex-linked recessive lethal mutations in two different studies in *Drosophila melanogaster*.

Regarding the key characteristics "alters DNA repair or causes genomic instability", "induces oxidative stress", "induces chronic inflammation", and "alters cell proliferation, cell death, or nutrient supply", there was a paucity of available data for each characteristic.

There was one study regarding the key characteristic of carcinogens "alters DNA repair or genomic instability", which showed that dimethyl hydrogen phosphite caused a significant increase in unscheduled DNA synthesis in rodent primary liver cells.

The mechanistic evidence is suggestive for the key characteristic of carcinogens "induces chronic inflammation". Two in vivo studies in Fischer 344 rats were available. The first study observed chronic inflammation in the lungs of male rats and in female rats at a high dose, but not in male or female B6C3F$_1$ mice. The second study showed that dimethyl hydrogen phosphite caused subepithelial inflammation and occasional submucosal and interstitial oedema in the forestomach of male rats.

The mechanistic evidence is suggestive for the key characteristic of carcinogens "alters cell proliferation, cell death, and nutrient supply". There were two in vivo studies in Fischer 344 rats available. The first study showed an increased incidence of hyperplasia and squamous metaplasia (high dose only) in the lung, and of hyperplasia and hyperkeratosis in the forestomach in male rats and an increased incidence of hyperplasia in the lung and forestomach of female rats at a high dose. The second study showed lesions characterized by epithelial hyperplasia and hyperkeratosis epithelial hyperplasia in the forestomach of male rats.

Of note, dimethyl hydrogen phosphite had no effect on the activities of superoxide dismutase or glutathione *S*-transferase in several tissues but caused increased levels of nonprotein sulfhydryls and reduced carboxylesterase activity in the forestomach, as observed in one study in rodents. Carboxylesterase activity was also reduced in the lung.

No data were available for the other key characteristics.

Dimethyl hydrogen phosphite was found to be without effects relevant to the key characteristics of carcinogens in the assay battery of the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA, although the dimethyl hydrogen phosphite testing solution was considered problematic for use in the high-throughput assays.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of dimethyl hydrogen phosphite.

6.2 Cancer in experimental animals

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

6.3 Mechanistic evidence

There is *limited mechanistic evidence*.

6.4 Overall evaluation

Dimethyl hydrogen phosphite is *possibly carcinogenic to humans (Group 2B).*

6.5 Rationale

The Group 2B evaluation for dimethyl hydrogen phosphite is based on *sufficient evidence* for cancer in experimental animals. The *sufficient evidence* for cancer in experimental animals is based on an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in males and females of a single species in one study that complied with Good Laboratory Practice. The mechanistic evidence was *limited*. There is suggestive evidence for several key characteristics (genotoxicity, induction of chronic inflammation, and alteration of cell proliferation in experimental systems). The evidence regarding cancer in humans was *inadequate* because no studies were available.

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