Phosphonic acid, methyl-, dimethyl ester: Human health tier II assessment

08 March 2019

CAS Number: 756-79-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

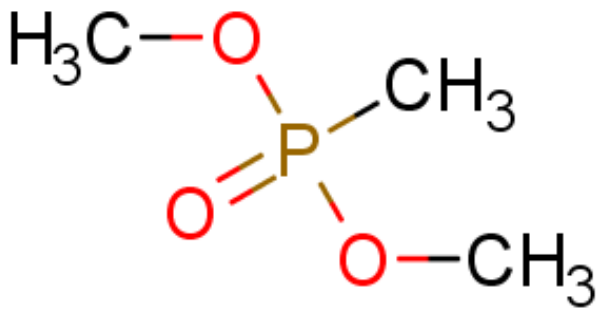
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	DMMP dimethyl methylphosphonate dimethoxymethylphosphine oxide
Structural Formula	
Molecular Formula	C3H9O3P
Molecular Weight (g/mol)	124.08
Appearance and Odour (where available)	Clear colourless liquid with a pleasant odor
SMILES	COP(C)(=O)OC

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified. There are restrictions on the importation and manufacture of the chemical in Australia (see ***Restrictions*** section). The chemical is identified as being commonly traded in Australia (ASNO, 2014).

International

The following international uses have been identified by the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Toxicology Program (NTP); European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; US Environment Protection Agency (US EPA) ChemView; and the US EPA Chemical and Product Categories (CPCat).

The chemical has reported commercial uses as:

- a flame retardant in urethane foams, polyester resins, building materials, furnishings, upholstery, transportation equipment and fittings, and in the electrical industry for cables and housings;
- a pre-ignition additive for petrol;
- an anti-foaming agent;
- a plasticiser;
- a stabiliser;
- a textile conditioner;
- an antistatic agent; and
- an additive for solvents and hydraulic fluids.

While some of these uses could have application in the domestic setting, the chemical is not listed in the US Department of Health & Human Services Household Products Database (US HPD).

The chemical has reported site-limited uses as a catalyst or intermediate in organic synthesis.

The chemical also has use as a warfare agent simulant.

Restrictions

Australian

Australia has ratified the Chemical Weapons Convention (CWC) (see ***Restrictions: International*** section). As the chemical is a scheduled chemical under this convention a number of restrictions apply in Australia. Facility operators, importers and exporters require permits for certain activities. Reporting requirements also apply.

Australia implements its CWC obligations through the following legislation and associated regulations.

- The Chemical Weapons (Prohibition) Act 1994;
- The Chemical Weapons (Prohibition) Regulations 1997;
- The Customs Act 1901;
- The Customs (Prohibited Imports) Regulations 1956 (5J); and
- The Customs (Prohibited Exports) Regulations 1958 (13E) (ASNO, 1994).

International

The chemical is listed on the Chemical Weapons Convention—Schedule 2, an international treaty that bans the 'development, production, acquisition, stockpiling, retention, transfer or use of chemical weapons by State Parties'. The chemical can only be 'used for purposes not prohibited' within the jurisdiction of member states (Organisation for the Prohibition of Chemical Weapons, 2005).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit of 5 mg/m^3 (100 ppm, maximum allowable concentration) in Belarus and Russia.

Health Hazard Information

Toxicokinetics

The majority of the administered dose was recovered in urine within 24 h indicating rapid absorption and excretion. The only metabolite detected in urine of male and female rats was methyl methylphosphonate. Unchanged DMMP was also detected in urine. Excretion is rapid with elimination half-lives between 3 and 6 h in rats. Most of the administered chemical was recovered in female urine within 24 h of administration. In males the recovery of the chemical and metabolites was lower; only 58–74 % of the administered dose was recovered within 24 h (Blumbach et al., 2000; REACH).

The chemical has been shown to bind to alpha-2μ globulin in male rats. In a 5-day study in F344 rats administered daily doses of 500 or 1000 mg/kg bw/day; there was a dose-dependent increase in alpha-2μ globulin in the cytosol of kidney cells in males but not in females. The increase in alpha-2μ globulin was accompanied by the formation of protein droplets in the proximal tubules of male rats and increased kidney weights. Further biochemical studies indicated that it was the unmetabolised chemical that bound the globulin (Blumbach et al., 2000).

Acute Toxicity

Oral

Based on the reported median lethal doses (LD50) in experimental animals, the chemical has low acute oral toxicity. The reported median lethal doses (LD50) from guideline and non-guideline studies in rats and mice are >5000 mg/kg bw/day. Clinical signs of toxicity included inactivity, unsteady gait, prostration, ataxia, muscular hypotonia, lying in unusual positions, hypoventilation, dyspnoea, diarrhoea and cyanosis. (NTP, 1987; US EPA 1992; US EPA, 2005; REACH).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The reported LD50 values from non-guideline studies considered to be well described and guideline studies in rats and rabbits are >2000 mg/kg bw/day. Reported LD50 values from non-guideline studies in rabbits were greater than >5000 mg/kg bw (US EPA, 2005). No clinical signs of toxicity were reported. Mild irritation was reported in some studies (US EPA, 1992; US EPA, 2005; REACH).

Inhalation

While the median lethal concentration (LC50) has not been completely established, the available data indicates that the chemical has low acute toxicity following inhalation exposure. The LC50 in rats is >2.589 mg/L (similar to guideline study). Other poorly described non-guideline studies have reported LC50 values >5 mg/L.

In an acute toxicity study conducted similarly to OECD TG 403, Sprague Dawley (SD) rats (10/sex/dose) were exposed to average aerosol concentrations of 1355 or 2589 mg/m^3 (reported as highest achievable concentration) of the chemical for 4 h and observed for 14 days. All animals survived the study. Clinical signs of toxicity included convulsions, eyeball protrusion, lying in unusual positions and ruffled fur. All animals recovered within 6–7 days. The LC50 was >2589 mg/m^3 (2.589 mg/L) (REACH).

In three non-guideline studies, rats were exposed to the chemical at nominal concentrations of 20.13–26.1 mg/L for 1 h and observed for up to 14 days. There was one female mortality in one of the studies. Clinical signs of toxicity included depression, ataxia, stained fur and piloreaction. The nature of the exposure is not reported; however, it is unlikely they were exposed to vapour due to the low vapour pressure of the chemical (0.05–0.13 kPa). The LC50 (nominal concentration) was >20 mg/L for 1 h. Under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), a 1 h LC50 can be converted to a 4 h value by dividing it by 4. This results in an LC50 >5 mg/L (US EPA, 2005).

In a saturated vapour test 5 male Fischer 344 rats and 5 male B6C3FI mice were exposed to a nominal concentration of DMMP of 3330 mg/m^3 (3.3 mg/L) for 6 hours. All animals survived the study. Reduced body weights were observed in rats (DTIC, 1984).

Corrosion / Irritation

Skin Irritation

The chemical may be slightly to moderately irritating to skin, following prolonged exposure. The effects are not sufficient to warrant hazard classification.

In a well-documented non-guideline study, the chemical (0.5 mL) was applied to shaved skin (occlusive) of Russian breed rabbits (3/sex) for 24 h. The skin was observed after 24, 48, and 72 h after treatment. The mean erythema scores for the individual rabbits were 0.3 in five rabbits and 0 in one rabbit. The erythema was fully reversible within 72 h. The score for oedema was 0 in all rabbits (REACH).

In an acute toxicity study in rats the chemical was applied to rat skin (occlusive) for 24 h. The application site was observed at 24, 48 and 72h. The mean erythema scores for each individual animal were 2 in one animal and 1.7 in the remaining 9 animals. The oedema scores were 1.7 in 5 animals, 2.3 in 3 animals, 2 and 2.7 in the last 2 animals. After 6 days the erythema and oedema had resolved (US EPA 1992; REACH).

In three studies, the chemical (0.5 mL) was applied to clipped skin of six albino rabbits with one abraded and one non-braded site for 24 h. Mild irritation was noted at 24 h in only two of the studies. Effects were reversed by 72 h (US EPA, 2005).

Eye Irritation

In eye irritation studies in rabbits, the chemical was found to be slightly to moderately irritating. Based on the reported irritation scores in a well documented study hazard classification is warranted (see ***Recommendation*** section). While not conclusive, overall the data indicated reversibility of effects.

In a study conducted similarly to OECD TG 405 (but with only an 8 days observation period), 0.1 mL of the chemical was applied to one eye of 6 albino Russian breed rabbits (3/sex) while the other eye served as the control. The irritation scores at the 3 different time-points (24, 48 and 72 h) were combined and averaged. The average irritation scores for the 3 individual rabbits were 2, 1.7, 1.7 for corneal opacity; 1, 0.3, 0.3 for iris irritation; 3, 2, 2.7 for conjunctival redness and 2.3, 1.5, 2 for chemosis. After 8 days the effects were reversed in 2 animals but remained in one animal with scores of 1 for corneal opacity; 2 for conjunctival redness and 1 for chemosis (REACH).

In a study conducted according to US EPA guidelines, 0.1 mL of the chemical was applied to one eye of 9 albino rabbits while the other eye served as the control. Six of the treated eyes remained unwashed for the duration of the study, while three of the treated eyes were rinsed with water. The animals were observed daily for seven days. The chemical caused mild conjunctival irritation in six unwashed eyes and one washed eye. The average scores for conjunctival irritation were 3.3, 0.7, and 0 for 24, 72 and 96 h, respectively (US EPA, 2005). No further information is available.

In a study conducted according to the US Federal Hazardous Substance Labeling Act , 0.1 mL of the chemical was applied to one eye of 6 albino rabbits while the other eye served as the control. The treated eyes remained unwashed during the 7 day observation period. The chemical caused mild irritation to the conjunctivae, but caused no irritation to the cornea or iris (US EPA, 2005). No further information is available.

In another study conducted according to the US Federal Hazardous Substance Labeling Act, 0.1 mL of the chemical was applied to one eye of 6 albino rabbits while the other eye served as the control. The treated eyes remained unwashed during the 72 h observation period. Mild irritation to the conjunctivae and minimal chemosis was observed at 24 h. No irritation was observed beyond 24 h (US EPA, 2005). No further information is available.

Observation in humans

The chemical induced mild to moderate irritation in a human repeated insult patch test (HRIPT) after repeated applications of the chemical as a 10 % or 20 % aqueous solution (see ***Skin sensitisation: Observation in humans*** section).

Sensitisation

Skin Sensitisation

Based on the available data the chemical is not considered to be a skin sensitiser.

In a non-guideline non-adjuvant study, 10 male albino guinea pigs received 4 weekly intradermal injections 1 % DMMP in dimethyl phthalate. Two weeks after the induction the guinea pigs received a topical application of the chemical [~0.05 mL neat or 50 % v/v in / guinea pig fat/acetone/dioxane mixture)]. The application sites were evaluated 24 and 48 h after the challenge. After 24 h 2/10 rabbits displayed mild oedema with no reactions observed at 48 h. Similar responses were observed in 3/10 animals receiving the same treatment at challenge but no induction treatment. The chemical was considered negative for skin sensitisation (REACH).

In a skin sensitisation study with limited information available, 10 albino guinea pigs were exposed to 0.5 mL of 10 % w/v aqueous solution of the chemical for 5 h. Two weeks later the animals received a challenge dose of the chemical (concentration and time not reported). The chemical was reported to be a non-sensitiser (US EPA, 1992).

Observation in humans

No sensitisation reactions were observed in a HRIPT in 50 subjects (25 males and 25 females). The chemical was applied to human subjects under occlusion for 24 h, nine times. The first six applications were with 20 % DMMP in aqueous solution. The concentration was reduced to 10 % DMMP for the last three applications. Moderate irritation was observed by the sixth application with mild irritation observed for the final three applications. After application of a challenge dose (10 % DMMP) one subject had a skin reaction that did not persist past 24 h. The chemical was considered a non-sensitiser (US EPA 1992).

Repeated Dose Toxicity

Oral

Other than effects on the male reproductive system (see ***Reproductive toxicity*** section); based on the available information, repeated oral exposure to the chemical is not expected to cause serious damage to human health. The observed kidney effects in rats are likely to be related to male rat-specific alpha-2μ globulin and not relevant to humans (see ***Toxicokinetics*** section) (Blumbach et al., 2000; Hard et al., 2004).

In an oral study conducted similarly to OECD TG 408, F344 rats (10/sex/dose) received daily doses of the chemical by gavage at 0, 250, 500, 1000, 2000 or 4000 mg/kg bw/day, 5 days/week for 13 weeks. In the highest dose group (4000 mg/kg bw/day) no animals survived past the first week. At 2000 mg/kg bw/day mortalities occurred in 6/10 males and 3/10 females, the surviving rats in these groups had slightly reduced body weights. No clinical signs of toxicity attributable to the chemical were observed during the study. At 2000 mg/kg bw/day, relative liver weights were increased in both sexes and absolute liver weights were increased in males. Kidney effects (nephrosis and hyaline droplet degeneration) were increased in all dosed male groups; however, these lesions are related to male rat-specific alpha-2μ globulin and not relevant to humans (Hard et al., 2004). A decrease in the number of spermatogonia and primary spermatocytes was observed at 2000 mg/kg bw/day. A no observed adverse effect level (NOAEL) of 1000 mg/kg bw/day was reported based on increased mortality and liver effects (NTP, 1987; US EPA 2006; REACH).

In a similar study B6C3F1 mice (6–10/sex/dose) received daily doses of the chemical by gavage at 0, 250, 500, 1000, 2000, 4000 or 8000 mg/kg bw/day, 5 days/week for 13 weeks. At doses of ≥4000 mg/kg bw/day survival was low. No mortality was observed in the other dose groups. No treatment-related clinical signs of toxicity, changes in body weight gain or macro- or microscopic lesions were observed. The reported NOAEL value was 2000 mg/kg bw/day based on increased mortality at the higher doses (NTP, 1987; US EPA, 2006).

In a feeding study, SD rats (20–25/sex/dose) received the chemical in the diet at 0, 1000, 3000 or 10000 ppm for 3 months. After the treatment period, 5 females and 5 males from the control and high dose groups (recovery groups) were maintained without treatment for 4 weeks. No treatment-related mortality was observed during the study or recovery period. No clinical signs of toxicity were observed apart from an effect on neuromuscular function in males of the highest dose group. This effect was partly reversed in the recovery group. Body weights and food intake were comparable between all groups. No adverse effects on clinical chemistry, haematology or urinalysis were reported during the main study or recovery period. There was a dose-related increase in absolute and relative kidney weights in male rats, as well as a slight increase in liver weights at the highest dose. Dose-dependent renal tubular regeneration was seen in all treated groups (number of males and females not specified). Intracellular inclusions and minimal centrilobular hepatocellular hypertrophy were observed at all doses. The kidney and liver effects were partly reversible in the recovery group. A lowest adverse effect level (LOAEL) of 1000 (equivalent to 65–71 mg/kg bw/day) was reported based on kidney and liver effects (REACH).

In a 4 week oral gavage study conducted similarly to OECD TG 407, SD rats (5–10/sex/dose) received the chemical in diet at 0, 2000, 6000 ppm or 20000 ppm. Daily average intakes were reported as 0, 178, 535 or 1790 mg/kg bw. From the highest dose group 5 males and 5 females were kept for observation for another 4 weeks (recovery period). No treatment-related effects were observed on survival, body weight, food consumption, the incidence of clinical signs, haematology, clinical chemistry, urinalysis or ophthalmoscopic findings. Absolute and relative kidney weights were increased in males fed the highest dose and in females receiving the two highest doses. All treated male rats displayed signs of nephropathy consistent with rat-specific alpha-2μ globulin binding which is not relevant to humans (Hard et al., 2004). Absolute and relative liver weights were significantly elevated in males at 20000 ppm; however, this was not associated with any histopathological findings. Therefore the increased

liver weights were considered adaptive and an NOAEL of 20000 ppm (1790 mg/kg bw/day) excluding nephropathy was reported (US EPA, 2006; REACH).

In oral carcinogenicity studies in rats and mice (see ***Carcinogenicity*** section), effects on survival and body weights were observed. No compound-related clinical signs were reported. Male rats displayed nephropathy consistent with male rat-specific alpha-2μ globulin binding. (Hard et al., 2004, NTP 2007).

Dermal

No data are available.

Inhalation

Based on the limited available information, it is not possible to determine whether repeated inhalation exposure to the chemical is likely to cause serious effects to human health.

In a non-guideline study F344 rats (85/sex/dose) were continuously exposed 0, 25 or 250 ppm (0, 127 and 1269 mg/m^3) DMMP for 90 days. Mortality was significantly increased in males. Body weight gain was reduced in male rats at both doses and in females exposed to 250 ppm. Red blood cell counts, haematocrit and haemoglobin levels were reduced in both male and female rats exposed to the high concentration. These changes were not fully reversible in male rats after a 3 and 12 month recovery period. Liver and kidney weights were significantly increased in both sexes at 250 ppm and in males exposed to 25 ppm. The liver and kidney changes persisted during a 3 month recovery period in males (but not in females) exposed to the highest concentration. Reduced testes weight and testicular atrophy was observed at the highest concentration. Results from histopathological examinations of the organs were not reported (DTIC, 1984).

Genotoxicity

In general available data from in vitro genotoxicity studies indicate that the chemical does not induce point mutations in bacteria; however, it is clastogenic in some mammalian cell assays. The chemical was mostly positive in in vivo genotoxicity assays. Due to mainly positive findings in mammalian cells and in vivo genotoxicity assays, including heritable germ cell tests, classification is warranted (see ***Recommendation*** section).

In vitro

The chemical was:

- negative in multiple point mutation studies in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537 concentrations up to 10000 μg/plate, with and without metabolic activation;
- positive gene mutation studies in the thymidine kinase (tk) locus in L5178Y mouse lymphoma at doses above 3.0 μl/mL (dose-dependent) without metabolic activation and with metabolic activation at doses above 5.0 μl/mL (dose-dependent) (NTP, 1987; US EPA, 2005);
- negative in a hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene mutation assay in Chinese hamster ovary (CHO) cells in the absence of activation (NTP,1987; US EPA 2006)
- negative in a chromosome aberration assay in Chinese hamster ovary (CHO) cells at concentrations at doses up to 22000 μg/mL with and without metabolic activation. In another study positive results were observed only at the top dose of 1000 μg/mL in the absence of activation (NTP, 1987; US EPA 2006)
- negative in sister chromatid exchange assay in CHO cells tested at concentrations as high as 1 mg/mL in one assay, but positive in another assay, both in the absence (over a concentration range of 0.16-11 mg/mL) and presence (at 1.1-22 mg/mL) of metabolic activation (NTP, 1987; US EPA 206). and
- positive in a chromosome aberration and sister chromatid exchange assay in L5178 mouse lymphoma cells at doses between 5–45μL/mL in the presence and absence of a metabolic activating system. The mutagenic activity of the chemical

was dose-dependent (US EPA, 2005).

The chemical was positive in a mammalian cell transformation test in normal BALB/3T3 cells, exposed to the chemical at 0.625 µL/mL–10 µL/mL. The increase in transformation capability was small (1.7 times control), but dose-dependent and statistically significant (US EPA, 2005). However, in another mammalian cell transformation test in BALB/3T3 cells no transformation capability was noted at concentrations up to 100 µg/mL (Sivak, 1983).

In vivo

The chemical was:

- negative in mammalian bone marrow chromosomal aberration test in male SD rats that received either a single dose or five consecutive doses at 556–5000 mg/kg bw/day (US EPA, 2005).
- positive in a sex-linked recessive lethal test in *Drosophila melanogaster* (23500 ppm in diet). Reciprocal translocations were not induced (NTP, 1987);and
- negative in a sex-linked recessive lethal test in *D. melanogaster* (dose not reported) (US EPA 2005).

The chemical had dominant lethal effects in male mice and rats. Treatment with the chemical at 1000 or 2000 mg/kg bw/day for 4, 8, or 12 weeks in mice or 250–2000 mg/kg bw day for 90 days in rats, caused increased numbers of dead implants (resorptions) indicative of increased dominant lethal mutations (see ***Reproductive toxicity*** section) (Dunnick, 1984a–b; NTP 1987).

In silico

The (Q)SAR modelling for genetic toxicity using the OECD QSAR Toolbox (version 4.2) indicated that there were alerts for both in vitro and in vivo mutagenicity as well as a protein binding alert for chromosomal aberration.

The (Q)SAR profiling indicated that the chemical is a weak alkylating agent. The alkylating activity of organophosphorus compounds is believed to be the basis of their mutagenicity (US EPA, 1982).

Carcinogenicity

There is limited evidence of carcinogenic potential; however, based on a significant positive trend and significant increases over concurrent and historical controls for the incidence of mononuclear cell leukemia in male rats, hazard classification is warranted (see ***Recommendation*** section).

In a 2-year carcinogenicity study, F344 rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) received the chemical by gavage at 0, 500 or 1000 mg/kg bw/day (rats) and 0, 1000 or 2000 mg/kg bw/day (mice) in corn oil, 5 days a week for 103 weeks. Mean bodyweights were reduced in both rats and mice receiving the high dose. Survival was reduced in male rats at both doses and in females receiving the high dose. The decreased survival rate was partly attributed to kidney toxicity of the chemical. The survival rate in mice was low; however, this was mainly due to fighting in male mice and a dosing error.

The incidence of mononuclear cell leukaemia in male rats receiving 0, 500 or 1000 mg/kg bw/day were 10/50 (20 %), 11/50 (22 %), and 17/50 (34 %), respectively. The increase in leukaemia was statistically significant at the highest dose. Staging of the leukemia indicated that most of the tumours in high dose males were stage 3 (lethal leukemia). Historical data from NTP studies indicate that mononuclear leukaemia is common in the F344 rat strain with an incidence of 21.4 ± 9 % in control animals (corn oil gavage) (Haseman et al., 1992). Marginal increases in pheochromocytomas, oral squamous cell papillomas or carcinomas (combined), thyroid adenomas or carcinomas (combined) and mesotheliomas in the tunica vaginalis were observed, but not considered clearly treatment-related (NTP, 1987). Male rats also had an increased incidence of renal tumours; however, these can be attributed to alpha-2µ globulin and not considered relevant to humans (Hard et al., 2004). There was no clear evidence of carcinogenicity in female rats, or male and female mice (Dunnick, 1988; US EPA; 2006).

Reproductive and Developmental Toxicity

The chemical caused adverse effects on the reproductive system of male rats. The quality of the sperm in male rats was decreased at doses ≥1000 mg/kg bw/day. Effects observed were similar to those induced by trimethylphosphate (TMP—CAS

No. 512-56-1). Resorptions indicative of dominant lethal effects occurred at doses of ≥250 mg/kg bw/day in rats and at ≥1000 mg/kg bw/day in mice (Dunnick et al., 1984a-b). Therefore, hazard classification is warranted (see ***Recommendation*** section). The chemical does not show specific developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

Reproductive toxicity

In a reproductive toxicity study, male F344 rats received the chemical by gavage at doses of 0, 250, 500, 1000 or 2000 mg/kg bw/day in water, 5 days a week for 90 days. On day 84 each treated male was mated with two untreated females. Males were sacrificed on day 90 and females on day 100. The treatment did not affect the survival of male rats. There was a dose-related decrease in sperm count and an increase in sperm-head abnormalities, which was statistically significant at the highest dose (2000 mg/kg bw/day). Sperm motility was significantly decreased at doses ≥1000 mg/kg bw/day. The majority of the rats in the highest dose group had testicular lesions characterised by lack of spermatogenesis and degeneration, vacuolisation, and necrosis of cells in the seminiferous tubules. Morphologic abnormalities in sperm from the group of the highest dose rats included headless sperm or sperm without or blunt hook. Plasma levels of luteinising hormone (LH) and follicle stimulating hormone (FSH) were not altered in treated animals. Males of the highest dose-group (2000 mg/kg bw/day) were infertile. In the other dose groups the fertility index was 70, 75, 60 and 40 % for 0, 250, 500 and 1000 mg/kg bw/day, respectively. Resorptions were increased at all doses in a dose-dependent manner, indicative of a dominant lethal effect (see ***Genotoxicity*** section). The percentage of resorptions in the control group was 6.1 % and increased to 14.9, 37.8, and 79.1 % in the 250, 500, and 1000 mg/kg bw/day groups, respectively. The LOAEL for dominant lethal effects in this study is 250 mg/kg bw/day based on increased resorptions in untreated females mated with treated males. The NOAEL for paternal toxicity is 500 mg/kg bw/day based on reduced on sperm motility at 1000 mg/kg bw/day (Dunnick et al., 1984a, US EPA 2005 & 2006); REACH). .

In another reproductive study male B6C3F1 mice were treated with 0, 250, 500, 1000, and 2000 mg/kg of the chemical by gavage 5 days per week for 13 weeks. After 4, 8 and 12 weeks of treatment the male mice were mated with untreated CD-1 female mice. Some mice were kept for an additional 15 weeks without chemical treatment an then mated with untreated CD-1 female mice. Increased numbers of resorptions and decreased numbers of live foetuses were observed at 1000 mg/kg bw/day and 2000 mg/kg bw/day, indicative of dominant lethal effects (see ***Genotoxicity*** section). Effects on resorptions appeared reversible during the 15 week recovery phase. No sperm abnormalities were seen in the male mice (Dunnick, 1984b; US EPA 2006).

In a 12-week study 49 male F344 rats received the chemical by gavage 1750 mg/kg bw/day in tap water; 14 control rats received tap water only. Groups of rats were euthanised and examined for microscopic lesions after 3, 4, 5, 7, 9 and 12 weeks. After the fifth week of treatment, body weights were reduced and epididymal weight gain impaired. Histopathological changes including decreased sperm density and abnormalities in sperm and Sertoli cells were observed from week 5 and increased in incidence and severity over time. The chemical also affected sperm development; spermatids were located in the wrong section of tubules in relation to the developmental stage (anachronistic spermiation). After 14 weeks of recovery without treatment approximately 80 % of the semiferous tubules appeared normal (Chapin et al., 1984; US EPA 2006).

In a spermatogenesis study 60 SD rats were administered 1750 mg/kg bw/day of the chemical for up to 12 weeks. Evidence of necrotising spermatids (multi-nucleated giant cells) was apparent after 5 weeks, but had declined by 7 weeks. Abnormalities in the form of cytoplasmic vacuolisation were observed in Sertoli cells of treated animals (Cho et al., 1994).

In a 90-day inhalation toxicity study (see ***Repeated dose toxicity*** section) male rats exposed to 250 ppm had reduced testicular weight both after 90 days and 3–12 months post exposure. The lower exposure concentration (25 ppm) had no effect on testes weight (DTIC, 1984).

Developmental toxicity

In a non-guideline developmental study, pregnant SD rats (25/dose) were administered the chemical in 2 % carboxymethylcellulose (CMC) by gavage at 0, 100, 1000, 2000 mg/kg bw/day over the period gestation days (GD) 6–15, and euthanised on GD 21. Feed intake was reduced at 1000 mg/kg bw/day. At 2000 mg/kg bw/day maternal body weight and feed intake were both reduced. Reduced foetal weight and delayed ossification of the skeleton were observed at doses ≥1000 mg/kg bw/day. No other foetal effects were reported. The NOAEL for maternal and developmental toxicity were reported as 100 mg/kg bw/day (US EPA, 2005 & 2006; REACH).

In a follow-up study, pregnant SD rats (25/dose) were administered the chemical in 2 % CMC by gavage at 2000 mg/kg bw/day over the period GD 6–15 or 2500 mg/kg bw/day for GD 6–10. Both doses reduced food consumption and the higher dose reduced maternal body weight gain. Foetal body weight gain and ossification and were delayed at both doses. No gross skeletal

abnormalities were observed at 2000 mg/kg bw/day. A few effects observed at the highest dose were considered to be in the normal range for the strain of rat (US EPA, 2005 & 2006; REACH).

In a developmental toxicity 50 pregnant CD-1 mice were administered the chemical in corn oil at 0 or 4175 mg/kg bw/day on GD 6–13. The treatment had no effect on dams, the number of pups per litter, pup survival, or foetal body weight gain. Pup birth weights were significantly lower in the treated group compared to controls (US EPA, 1992).

Other Health Effects

Neurotoxicity

Unlike TMP (NICNAS) neurotoxic effects were not observed in repeated dose toxicity studies even when tested at relatively high doses.

Organophosphorous compounds are often associated with anticholinesterase activity. The chemical displayed low anticholinesterase activity but only at high doses. The chemical did not cause organophosphate induced delayed neuropathy in chickens (OPIDN).

In a cholinesterase activity study, SD rats (5/sex/dose) received daily doses of the chemical by gavage at 0, 1, 10, 100 or 1000 mg/kg bw/day for 3 days. No clinical signs of toxicity were observed. At the highest dose (1000 mg/kg bw/day) the activity of plasma cholinesterase was suppressed by approximately 30 % in males and 40–50 % in females. No effects on cholinesterase were noted at the other dose levels. Therefore the NOAEL for cholinesterase depression is 100 mg/kg bw/day (US EPA, 1992).

No delayed neurotoxicity was seen in hens observed for 21 days following oral administration of 11999 or 3998 mg/kg bw initially and after 21 days (US EPA, 1992).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects including reproductive toxicity and genotoxicity and local effects of eye irritation. There is limited evidence of carcinogenicity at high doses.

Public Risk Characterisation

The uses of the chemical in Australia are unknown. While import of the chemical is subject to some controls under the CWC (see ***Restrictions*** section), the chemical is reported to be commonly traded in Australia. The chemical has reported uses overseas as a fuel additive and as a flame retardant in a wide range of products. Given the uses identified for the chemicals, it is unlikely that the public will be exposed directly to the chemical from using consumer products.

The chemical is not listed in the US Household Products Database and in Europe the chemical is registered for use as an intermediate and processing aid (REACH).

Although it is expected that the chemical will be bound within articles or coated surfaces, consumers may be directly exposed to the chemical that is released from articles through, for example, abrasion or dissolution. While many phosphate flame retardants were commonly detected in household dust, there is currently no evidence of DMMP being present in house dust (Cequier et al., 2014; He et al., 2018; Wong et al., 2018; Shoeib et al., 2019). The total levels of phosphate esters that have been measured in house dust are relatively low. The human exposure from indoor environments in Australia to nine organophosphate flame retardants was estimated to 14 ng/kg bw/day. Therefore, the risk of adults and children being exposed to levels of the chemical leading to adverse health effects is considered to be very low.

Should additional information to better characterise exposure become available, further assessment may be required.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) (see ***Recommendation*** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)
Genotoxicity	Not Applicable	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility - Cat. 1B (H360F)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the Managing risks of hazardous chemicals in the workplace—Code of practice available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

ensuring that hazardous chemicals are correctly classified and labelled;

ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the Preparation of safety data sheets for hazardous chemicals—Code of practice and Labelling of workplace hazardous chemicals—Code of practice, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

Australian Safeguards and Non-proliferation Office (ASNO), 2014 The Chemical Weapons Convention Available at https://dfat.gov.au/international-relations/security/non-proliferation-disarmament-arms-control/chemical-weapons/cwc/Documents/Chemical_Weapons_A%20Guide.pdf

Blumbach K, Pähler A, Deger HM and Dekant, W, 2000. Biotransformation and male rat-specific renal toxicity of diethyl ethyl- and dimethyl methylphosphonate. Toxicological Sciences, 53(1) pp. 24-32.

Cequier E, Ionas C, Covaci A, Marcé RM, Becher G and Thomsen C, 2014. Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. Environmental science& technology, 48(12) pp.6827-6835.

Chapin RE, Dutton SL, Ross MD, Sumrell BM and Lamb IV JC, 1984. Development of reproductive tract lesions in male F344 rats after treatment with dimethyl methylphosphonate. Experimental and molecular pathology, 41(1) pp. 126-140.

Cho NH and Park C, 1994. Effects of Dimethyl Methylphosphonate (DMMP) and Trimethylphosphate (TMP) on. Yonsei Medical Journal, 35(2).

Defence Technical Information Center, Toxic Hazards Research Section Annual report 1985 Accessed January 2019 at https://discover.dtic.mil/

Dunnick JK, Gupta BN, Harris MW and Lamb IV JC, 1984a. Reproductive toxicity of dimethyl methyl phosphonate (DMMP) in the male Fischer 344 rat. Toxicology and applied pharmacology, 72(3), pp.379-387.

Dunnick JK, Solleveld HA, Harris MW, Chapin R and Lamb IV JC, 1984b. Dimethyl methyl phosphonate induction of dominant lethal mutations in male mice. Mutation Research/Genetic Toxicology, 138(2-3) pp. 213-218.

Galleria Chemica. Accessed January 2019 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed January 2019 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Haseman JK and Rao GN, 1992. Effects of corn oil, time-related changes, and inter-laboratory variability on tumor occurrence in control Fischer 344 (F344/N) rats. Toxicologic pathology, 20(1) pp 52-60.

He C, Wang X, Thai P, Baduel C, Gallen C, Banks A, Bainton P, English K and Mueller JF, 2018. Organophosphate and brominated flame retardants in Australian indoor environments: Levels, sources, and preliminary assessment of human exposure. Environmental Pollution, 235 pp. 670-679.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) . Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Phosphoric acid, trimethyl ester (CAS No. 512-56-1). Available at http://www.nicnas.gov.au

National Toxicology Program (NTP) 1987. Toxicology and carcinogenesis studies of dimethyl methylphosphonate in F344/N rats and B6C3F1 mice. Accessed January 2019 at https://ntp.niehs.nih.gov

Organisation for the Prohibition of Chemical Weapons 2005. Convention on the prohibition of the development, production, stockpiling and use of chemical weapons and on their destruction. Accessed January 2019 at https://www.opcw.org/chemical-weapons-convention/download-the-cwc/

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Registration dossier for dimethyl methyl phosphonate (CAS No. 756-79-6). Accessed December 2018 at https://echa.europa.eu/

Safe Work Australia (SWA). Hazardous Chemicals Information System (HCIS). Accessed November 2018 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Shoeib T, Webster GM, Hassan Y, Tepe S, Yalcin M, Turgut C, Kurt-Karakus PB and Jantunen L, 2019. Organophosphate esters in house dust: A comparative study between Canada, Turkey and Egypt. Science of The Total Environment, 650 pp. 193-201.

Sivak A, 1983. Evaluation of Dimethyl Methylphosphonate and Exo-Tetrahydrodi-(Cyclopentadiene) in a Battery of in Vitro Short-Term Assays. LITTLE (ARTHUR D) INC CAMBRIDGE MA.

US Department of Health and Human Services, Household Products Database (HPD). Accessed January 2019 at https://hpd.nlm.nih.gov/advancedsearch.htm

US EPA, Health advisory for dimethyl methylphosphonate (DMMP), 1992 Accessed January 2019 at https://nepis.epa.gov

US EPA, HPV Robust Summaries for dimethyl methylphosphonate, 2005 Accessed January 2019 https://www.echemportal.org/echemportal/substancesearch/substancesearch_execute.action

US EPA, Provisional Peer Reviewed Toxicity Values for Dimethyl methylphosphonate, 2006 Accessed January 2019 at https://cfpub.epa.gov/ncea/pprtv/documents/Dimethylmethylphosphonate.pdf

Wong F, de Wit CA and Newton SR, 2018. Concentrations and variability of organophosphate esters, halogenated flame retardants, and polybrominated diphenyl ethers in indoor and outdoor air in Stockholm, Sweden. Environmental Pollution, 240 pp. 514-522.

Last update 08 March 2019

Share this page