Phosphorous acid, trimethyl ester: Human health tier II assessment

21 April 2016

CAS Number: 121-45-9

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.

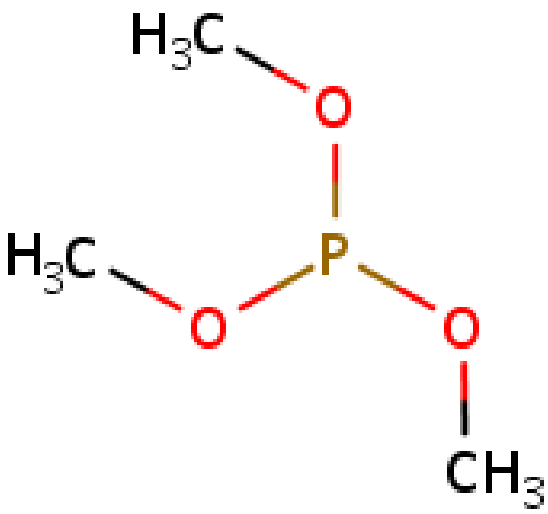
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	trimethyl phosphite trimethoxyphosphine TMP
Structural Formula	
Molecular Formula	C3H9O3P
Molecular Weight (g/mol)	124.08
Appearance and Odour (where available)	Colourless liquid with pungent, oily, pyridine-like odour
SMILES	COP(OC)OC

Import, Manufacture and Use

Australian

The chemical was reported under previous mandatory and/or voluntary calls for information. No volume or use data have been identified.

International

The following international uses have been identified through Galleria Chemica; the United States (US) High Production Volume (HPV) Challenge Program; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the American Conference of Governmental Industrial Hygienists (ACGIH).

The chemical has reported commercial use as a fireproofing agent in the production of textiles.

The chemical has reported site-limited uses, including as:

- an intermediate in flame-retardant polymer manufacturing for polyurethane foams; and
- a liquid phosphorous source for phosphosilicate glass manufacturing.

The chemical has reported non-industrial use as an intermediate in manufacturing pesticides and pharmaceuticals.

Restrictions

Australian

The chemical is listed on the following (Galleria Chemica):

- *Customs (Prohibited Imports) Regulations 1956*—Part 4 of Schedule 11, whereby importation of the chemical into Australia is prohibited unless written permission has been given by the Minister for Foreign Affairs (or an authorised person) and the permission is produced to a Collector; and
- *Chemical Weapons (Prohibition) Act 1994*—Schedule 3, whereby a permit is required to operate a facility that produces more than 30 tonnes of the chemical annually and the facility is subject to an international compliance inspection.

International

The chemical is listed on the Chemical Weapons Convention—Schedule 3, 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 Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

The chemical has an exposure standard of 10 mg/m^3 (2 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 2.6 mg/m^3 (0.5 ppm) TWA in different countries such as Canada (Yukon), Denmark, Iceland and Norway;
- an exposure limit of 5 mg/m^3 TWA in Poland;
- an exposure limit of 10 mg/m^3 (2 ppm) TWA in different countries such as Canada (Alberta, British Columbia, Quebec, Saskatchewan), France, Greece, Indonesia, Ireland, Malaysia, Mexico, Singapore, South Africa, Spain, Switzerland, Taiwan, the United Kingdom and the US (California, Hawaii, Minnesota, Tennessee, Vermont, Washington);
- a short-term exposure limit (STEL) of 7.8–10 mg/m^3 (1.5–2 ppm) in Canada (Yukon) and Poland;
- an STEL of 20–25 mg/m^3 (4–5 ppm) in Canada (Saskatchewan), Mexico and the US (Hawaii, Washington).

Health Hazard Information

Toxicokinetics

The available toxicity data indicate that the chemical may be absorbed following oral, dermal and inhalation exposure (US EPA, 2012).

The chemical reacts rapidly with water and has high vapour pressure. It is hydrolysed to dimethyl phosphite and methanol and the 'hydrolysis reaction occurs in minutes over a range of pH values' (US EPA, 2010).

Acute Toxicity

Oral

Based on the available data in rats, the chemical has moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section).

The following median oral lethal dose (LD50) values were reported (US EPA, 2012; RTECS):

- 1350 mg/kg bw in Sprague Dawley (SD) rats;
- 1500–2240 mg/kg bw in Wistar rats;
- 1600 mg/kg bw in rats (strain not indicated); and
- 4280 mg/kg bw in ICR mice.

Dermal

As the available LD50 data indicate a wide range, it is not possible to derive a conclusion on the acute dermal toxicity of the chemical.

Dermal LD50 values of 934–7500 mg/kg bw were reported in New Zealand White rabbits (ACGIH, 2001; US EPA, 2012). The tests may have been conducted using the chemical with varying impurity levels.

Inhalation

Based on the available data, the chemical has low acute inhalation toxicity.

The following median lethal concentration (LC50) values were reported (US EPA, 2010; US EPA, 2012; RTECS):

- <6450 ppm/6-hours (<32.7 mg/L/6-hours) in male Wistar rats and male Swiss albino mice;
- >6450 ppm/6-hours (>32.7 mg/L/6-hours) in male English short-hair guinea pigs;
- >9000 ppm/4-hours (>45.7 mg/L/4-hours) in male rats (strain not indicated);
- >10000 ppm/4-hours (>50.7 mg/L/4-hours) in rats (strain not indicated); and
- 35885 ppm/1-hour (182 mg/L/1-hour) in rats (strain not indicated).

Corrosion / Irritation

Respiratory Irritation

Limited information indicates respiratory irritation from inhalation exposure. However, the available information is insufficient to warrant hazard classification.

In acute inhalation and repeated dose inhalation toxicity testing, respiratory irritation, respiratory distress, foamy fluid in the lungs and histological evidence of lung inflammation have been reported (ACGIH, 2001; US EPA, 2010).

Skin Irritation

Based on the available data, the chemical may be irritating to skin. However, the available information is insufficient to classify the chemical as hazardous.

In a skin irritation study, New Zealand White rabbits (n = 6) were administered 0.5 g of the chemical (occluded) onto intact and abraded skin sites for 24 hours and observed for 72 hours after exposure. Mean scores for erythema (redness) and oedema (swelling) combined were 2.5 and 2.6 for intact and abraded skin, respectively (US EPA, 2012).

In a study identical to that described above, except for the addition of nitrogen (N_2) to the chemical to prevent hydrolysis, no irritation (erythema, oedema or eschar formation) was observed (US EPA, 2012).

In another study, 'moderately severe but persistent irritation' was reported when the chemical was applied to rabbit skin (ACGIH, 2001). No further details are available.

Eye Irritation

Based on the available data, the chemical may be irritating to eyes. However, the available information is insufficient to classify the chemical as hazardous.

In an eye irritation study, New Zealand White rabbits (n = 6) were administered 0.1 mL of the chemical into the conjunctival sac of one eye, and observed at one, 24, 48 and 72 hours, as well as seven days after administration. Iritis was observed at one hour, and conjunctivitis was observed at one and 24 hours (irritation scores are not available). All effects were reversible by the 48 hour observation time-point (US EPA, 2012). No further details were available.

In a study identical to that described above, except for the addition of N_2 to the chemical to prevent hydrolysis, no irritation was observed (US EPA, 2012).

Severe ocular irritation and swelling were also reported when the undiluted chemical was instilled into the eye of rabbits, but effects were reversible after 'several days' (ACGIH, 2001). No further details are available.

Observation in humans

The chemical was reported to irritate the eyes, skin and the upper respiratory system (HSDB). Further details are not available.

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause severe health effects from repeated oral exposure, except at high doses (>160 mg/kg bw/day).

In a repeated dose toxicity study, SD rats (n = 15/sex/dose) were administered the chemical (in corn oil) by oral gavage doses of 0, 40, 80 or 160 mg/kg bw/day for 90 days. The no observed adverse effect level (NOAEL) was 80 mg/kg bw/day, based on toxicity observed at the highest dose. This included seven deaths (four males and three females); significantly reduced body weight and food intake; and significantly increased absolute adrenal, brain and kidney weights. Effects on reproductive organs were also observed in male rats in the highest dose group (see **Reproductive and developmental toxicity** section) (US EPA, 2012).

In a 21-day study, SD rats (n = 5/sex/dose) received the chemical by oral gavage at doses of 0, 33, 164 or 328 mg/kg bw/day, and an NOAEL of 33 mg/kg bw/day was established based on reduced locomotor activity and body weights at ≥164 mg/kg bw/day. At the highest dose, four males and four females died during the study and stomach congestion was observed in all high dose animals during gross pathological examinations (US EPA, 2012).

In a 28-day study in SD rats (n = 6–12/sex/dose), an NOAEL of 60 mg/kg bw/day was established based on irreversible corneal opacity and significantly reduced body weight and food consumption at 250 mg/kg bw/day (J-CHECK, 1997).

Dermal

Based on the limited available data, the chemical is not considered to cause severe health effects from repeated dermal exposure.

In a 21-day study, the chemical was applied to intact or abraded skin of New Zealand White rabbits (n = 6/sex/dose) at 0, 300, 600 or 1200 mg/kg bw/day for six hours per day, before being washed off with warm water. There were deaths at all dose levels (1/12, 2/12 and 11/12 for the 300, 600 and 1200 mg/kg bw/day doses, respectively). Reduced locomotor activity was seen in animals exposed at 300 and 600 mg/kg bw/day; vocalisation and loss of the righting reflex at 600 mg/kg bw/day; and significantly reduced body weights at 1200 mg/kg bw/day. In animals exposed to the chemical on abraded skin, dose- and time-dependent erythema and oedema were observed. During necropsy, a dose-dependent increase in the incidence of spots on lungs was observed; this was associated with histopathological signs of lung congestion and oedema at 300 and 600 mg/kg bw/day. Liver cell swelling, degeneration and infiltration with oval (liver progenitor) cells was observed at 300 and 600 mg/kg bw/day (US EPA, 2012).

Inhalation

Based on the available 28-day studies, the chemical is considered to cause severe health effects from repeated inhalation exposure, warranting hazard classification (see **Recommendation** section). Dose-related ocular lesions have been observed in rats from 50 ppm, leading to irreversible cataracts at 600 ppm.

In three separate (but related) studies, SD rats (n = 10–36/sex/dose) were exposed (whole body) to the chemical vapour at 0–600 ppm (equivalent to approximately 0–3 mg/L) for six hours per day, five days per week for 28 days. The no observed adverse effect concentration (NOAEC) was 10 ppm (~0.05 mg/L) based on local effects observed at ≥50 ppm (~0.26 mg/L). Dose-related ocular lesions were observed during necropsy in rats exposed to the chemical vapour at ≥50 ppm, with mild inflammatory changes at 50 and 100 ppm; corneal opacity (reversible striate type) at 100 ppm; corneal opacity and cloudy eyes at 300 ppm; and irreversible cataracts at 600 ppm. Deaths were observed at ≥300 ppm (~1.48 mg/L), and body weights were reduced at 600 ppm. Clinical signs of toxicity included laboured breathing, lacrimation (tearing) and chromodacryorrhoea (porphyrin-stained tears) at ≥300 ppm; and reduced locomotor activity, reduced body temperature and closed eyes at 600 ppm. Absolute lung weights were increased at 600 ppm; gross lung abnormalities (e.g. discolouration) were observed across all treatment groups, but were present in higher incidences at 600 ppm; and histopathological changes in the lungs (inflammation and bronchopneumonia) were linked with the deaths that occurred at 600 ppm (US EPA, 2012).

Observation in humans

In workers (n = 179) exposed to the chemical in manufacturing plants at an average concentration of 0.3–4 ppm (occasionally up to 15 ppm), no ocular or other adverse health effects were reported (ACGIH, 2001).

Genotoxicity

The available information indicates that the chemical may have mutagenic effects in germs cells, but due to the lack of in vivo studies in mammals, the data are not conclusive.

Mixed results were reported for the chemical in several in vitro genotoxicity assays (US EPA, 2012):

- negative in several Ames tests in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 exposed to the chemical at 0.001–50 µL/plate, with or without metabolic activation;
- negative in gene mutation tests in *Saccharomyces cerevisiae* D4 exposed to the chemical at 0.001–5 µL/plate, with or without metabolic activation;
- positive in DNA damage and repair tests in *Escherichia coli* strains WP2 and WP100, and *S. typhimurium* strains TA1978 and TA1538 exposed to the chemical at 0.3–50 µL/plate, with or without metabolic activation; and
- positive in several mutagenicity assays in mouse lymphoma (L5178Y) cells exposed to the chemical at 0.18–3.2 µL/mL, with or without metabolic activation.

Two in vivo genotoxicity assays with *Drosophila melanogaster* gave positive results for the chemical (US EPA, 2012):

- induction of sex-linked recessive lethal mutations, induction of dominant lethal mutations and bithorax test of Lewis (induction of chromosomal aberrations and loss) in *D. melanogaster* exposed to 0.07 mL of the chemical as an aerosol in a 25 mL flask for 30 seconds; and
- induction of sex-linked recessive lethal mutations, induction of dominant lethal mutations, bithorax test of Lewis (induction of chromosomal aberrations and loss) and Y-chromosome loss in *D. melanogaster* exposed to 0.3 mL of the chemical in a 50 mL flask.

No other in vivo genotoxicity assays are available for the chemical.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The available data are insufficient to derive a conclusion on the developmental toxicity of the chemical; developmental effects were observed coinciding with maternal toxicity (weight loss). Specific effects on male reproductive organs were seen during repeat dose studies.

No reproductive toxicity studies are available for the chemical. In a repeated dose toxicity study, SD rats (n = 15/sex/dose) were administered the chemical (in corn oil) by oral gavage doses of 0, 40, 80 or 160 mg/kg bw/day for 90 days. Toxicity (seven deaths—four males and three females, as well as significantly reduced body weight and food intake) was observed at the highest dose. In all male rats that survived at the highest dose (n = 11), gonadal hypoplasia (underdevelopment) was observed and this was associated with reduced spermatogenesis (reduced spermatogonia size and number; fewer spermatocytes and spermatids) (US EPA, 2012). These effects were not observed in males that received the chemical at 80 mg/kg bw/day.

In a developmental study, pregnant SD rats (n = 25/dose) were administered the chemical (in corn oil) at 0, 16, 49, 164 mg/kg bw/day from gestation day (GD) 6–15, and euthanised on GD 21. In animals exposed at 164 mg/kg bw/day, maternal body weight was reduced in the first five days of dosing and on GD 20; pup development was affected, including long bone abnormalities, dilated ventricles and undescended testes; teratogenicity was observed in pups, including exencephaly (brain located outside the skull), spina bifida (exposed spinal cord), scoliosis (abnormal curvature of the spine) and cleft palate. These effects were not observed in pups from the groups that received the chemical at 16 and 49 mg/kg bw/day. The NOAEL for maternal and developmental toxicity was reported as 49 mg/kg bw/day (US EPA, 2012).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is systemic acute effects from oral exposure.

The chemical can also cause harmful effects following repeated inhalation exposure.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and inhalation exposure are implemented. 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 hazard classification of the chemical.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended 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 under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure through inhalation (Xn; R48/20)	May cause damage to organs through prolonged or repeated exposure through inhalation - Cat. 2 (H373)

[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 oral 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;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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.

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