Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1) (salt): Human health tier II assessment

27 November 2014

CAS Number: 55566-30-8

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.

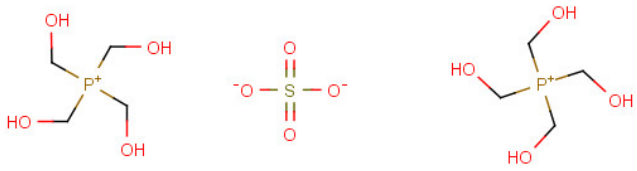
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Tetrakis(hydroxymethyl)phosphonium sulfate Magnacide 575 Tolcide
Structural Formula	
Molecular Formula	C4H12O4P.1/2O4S
Molecular Weight (g/mol)	406.28
Appearance and Odour (where available)	Light coloured liquid (75% THPS); Soft waxy solid (100% THPS)
SMILES	C(O)P{+}(CO)(CO)(CO).O{-}S(=O)(=O)O{-}.P{+}(CO)(CO)(CO)CO

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic use including in:

- flame retardants and fire preventing agents; and
- corrosion inhibitors.

The chemical has reported site-limited uses including in complexing agents and hydraulic fracturing.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was below 1000 tons.

International

The following international uses have been identified through Galleria Chemica and Substances and Preparations in the Nordic countries (SPIN).

The chemical has reported commercial use including as a tanning agent.

The chemical has reported site-limited uses including in industrial biocides and hydraulic fracturing.

The chemical has non-industrial use including as agricultural and non-agriculture pesticides and preservatives.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

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

No specific exposure standards are available.

International

Canada (Alberta, Nova Scotia, British Columbia), the American Conference of Government Industrial Hygienists (ACGIH), Italy and some South American countries have an occupational exposure limit of 2 mg/m^3.

Health Hazard Information

Toxicokinetics

Information about absorption, distribution and excretion of tetrakis(hydroxymethyl)phosphonium sulfate (THPS) is not available. Effects observed in acute and repeat oral and dermal toxicity studies indicate that THPS is absorbed through the skin and in the gastrointestinal tract.

In a THPS metabolism study in rats using ^{14}C-radiolabelled THPS, three metabolites of THPS (trihydroxymethyl phosphine oxide, bishydroxymethylphosphonic acid and possibly a formaldehyde adduct of the trihydroxy compound) were detected in urine. No unmetabolised THPS was found in the urine. No further details of the study are available (IPCS, 2000).

Acute Toxicity

Oral

A 72 % aqueous solution of THPS has moderate acute toxicity from oral exposure in rodents.

In gavage studies conducted by the United States National Toxicology Program (US NTP), Fischer 344N (F344/N) rats and B6C3F1 mice were administered 100, 200, 400, 800, or 1600 mg/kg bw THPS (72 % aqueous solution). The acute oral median lethal doses (LD50s) were 333 and 248 mg/kg bw in male and female rats, respectively. No LD50 was established for the mice (US NTP, 1987). Details of adverse effects observed in treated animals were not provided.

Dermal

THPS has low acute toxicity from dermal exposure in rats. No deaths were recorded following an application of 2000 mg/kg bw THPS to the skin of rats (Liggett & Allen, 1989). No further details were provided.

Inhalation

THPS has low acute toxicity by the inhalation route in rats. In rats, the 4-hour acute median lethal concentration (LC50) was 5.5 mg/L following nose-only exposure to aerosolised THPS (IPCS, 2000). Details of the study including any adverse effects noted in treated animals are not available.

Observation in humans

No data are available.

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The skin irritation potential of THPS cannot be sufficiently determined based on the variable results and the inadequate reporting of the available studies.

No dermal irritation was observed in New Zealand White rabbit skin when 0.5 mL of a 75 % aqueous solution of THPS solution was applied for four hours (Liggett, 1989). In another study, the chemical was applied to the shaved skin of Charles River-derived CD rats at 25, 250, or 500 mg/kg bw/day. The dosing had to be terminated due to the severity of the skin reactions after six days (Hill, 1989). No other details were available for these studies.

Eye Irritation

The chemical is a severe eye irritant in rabbits.

In an eye irritation test conducted in accordance with the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 405, application of 0.1 mL of 75 % THPS to New Zealand White rabbit eyes resulted in opacity, red colouration of the conjunctivae and considerable swelling. Although the Draize score was not reported in this study, on the basis of the observed effects, THPS was considered a severe eye irritant (Liggett, 1989b).

Observation in humans

No data are available.

Sensitisation

Skin Sensitisation

THPS is considered to be a skin sensitiser.

A 75 % aqueous solution of THPS was assessed for skin sensitisation using the Magnusson and Kligman Maximisation Test (OECD TG 406). Details of the study are not provided. Fourteen out of 20 animals challenged with the test substance were sensitised (Guest, 1994), demonstrating a sensitisation potential for THPS (IPSC, 2000).

Observation in humans

No data are available.

Repeated Dose Toxicity

Oral

In a repeated dose 14-day oral study, F344/N rats were administered 0, 12.5, 25, 50, 100, or 200 mg/kg bw/day THPS (72 % aqueous solution) by gavage. All rats that received 100 or 200 mg/kg bw/day died before the end of the study. Prior to mortality, animals showed tremors and partial loss of hind leg movement. Rats that received 50 mg/kg bw/day gained notably less weight than did the controls. No compound-related lesions were observed at necropsy.

In another oral gavage study, Charles River CD rats were administered 0, 6, 30, or 60 mg/kg bw/day THPS (75 % solution) for 28 days. Mortality (males only) was observed at the highest dose. Post-dose salivation, emaciation, hypoactivity, hunched posture, noisy breathing, urogenital staining and ptosis were observed in rats at the highest dose, while rats administered the mid dose (30 mg/kg bw/day) showed severe bodyweight loss (74 % in females and 52 % in males). A no observed adverse

effect level (NOAEL) of 4.5 mg/kg bw/day (active substance), based on severe body weight loss, was established in this study (Hill, 1989).

In a 13-week gavage study, F344/N rats were administered 0, 5, 10, 20, 40, or 60 mg/kg bw/day THPS (72 % aqueous solution). Three of 10 male rats that received 60 mg/kg bw/day died before the end of the study. Final mean body weights were 5 %, 15 % and 22 % lower than those of the vehicle controls for males that received 20, 40 or 60 mg/kg bw/day and from 7 % to 19 % lower for all groups of dosed female rats. Diarrhoea was seen in all groups of dosed rats during weeks three and four.

Vacuolar degeneration of the hepatocytes occurred in all males receiving 10 mg/kg bw/day of THPS or more, in 5/10 females receiving 20 mg/kg bw/day and in all females receiving 40 or 60 mg/kg bw/day. The severity of this lesion was greatest in the 60 mg/kg bw/day group. Lymphoid depletion in the spleen or thymus was observed in the three males in the 60 mg/kg bw/day group that died before the end of the study. Bone marrow hypoplasia was diagnosed in 3/10 male and 4/10 female rats in the 60 mg/kg bw/day groups. A NOAEL of 3.6 mg/kg bw/day (active substance), based on vacuolar degeneration of hepatocytes, was established in this study (US NTP, 1987).

In a chronic 104-week study, F344/N rats and B6C3F1 mice were administered 0, 5, or 10 mg/kg bw/day THPS (72 % aqueous solution) by gavage. Decreased survival of males at the low dose (after week 102) and high dose (after week 67) was recorded. Both sexes showed dose-related increased incidence of hepatocellular cytoplasmic vacuolisation. Focal hyperplasia of the adrenal medulla was noted, but the occurrence was statistically unrelated to dose. The lowest observed adverse effect level (LOAEL) was 3.6 mg/kg bw/day (active substance) and a NOAEL was not established (US NTP, 1987).

Dermal

In a repeated dose dermal study, details of which are not provided, THPS was applied daily to depilated dorsal skin of male ICR mice for 14 days at doses of 125, 350, 700, or 1000 mg/kg bw/day. The effects observed were decreased bodyweight (dose groups not specified), paralysed back muscles at 700 and 1000 mg/kg bw/day, and superficial necrosis at all doses (IPSC, 2000). No other details were provided. A dermal LD50 for THPS could not be established from this study.

Inhalation

No data are available.

Observation in humans

No data are available.

Genotoxicity

The chemical THPS was not mutagenic when tested in the *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of S9 from the livers of Aroclor-1254-treated rats (Dillon & Riach, 1990).

When tested in the mouse lymphoma assay, THPS caused mutations both in the presence and absence of S9 from Aroclor-treated rats (Riach, 1996). The US NTP (1987) also reported positive results for THPS in the mouse lymphoma assay in the absence of S9.

High levels of structural chromosomal aberrations were detected at the metaphase in Chinese hampster ovary (CHO) cells treated with THPS in the presence or absence of S9 from the livers of Aroclor-treated rats (Leddy, 1990). Anaphase analysis of THPS-treated CHO cells also showed chromosomal aberrations along with abnormal spindles (Coutino, 1979).

The results of an in vitro assay for unscheduled DNA synthesis in a primary culture of rat hepatocytes were negative (Riach, 1994).

In vivo assays of the cytogenetic effects of THPS in Swiss ICR mice dosed orally or dermally with the chemical did not show any increase in bone marrow micronuclei or chromosomal aberrations (Connor et al., 1980).

In a dominant lethal assay, male Swiss (ICR) mice were dosed once with up to 1000 mg/kg bw. There was no evidence to suggest that THPS produced dominant lethal mutations (IPCS, 2000).

In another dominant lethal study in rats, gavage doses of 5, 10 or 15 mg/kg bw/day were given to males for 10 weeks. After mating, investigation of the pregnant females indicated no dominant lethal mutations (Clode, 1996).

In conclusion, although some in vitro studies showed mutagenic effects for THPS, in vivo cytogenetic studies and dominant lethal assays produced negative results. Based on the above observations, THPS is not considered to be genotoxic.

Carcinogenicity

Carcinogenicity studies for THPS are not available. In the 104-week gavage studies by the US NTP, F344/N rats and B6C3F1 mice were administered 72 % THPS solution at doses of 0, 5 or 10 mg/kg bw/day. In male rats, increased incidence of mononuclear cell leukaemia was observed at the low dose compared with controls; and in male mice, increased incidence of malignant lymphomas was observed at the low dose compared with controls. The US NTP considered the incidence of the tumours as marginal and established that the effects were not considered biologically related to chemical exposure since no dose-response relationship was observed. In addition, the incidence of the lesions was variable in the control group. It was therefore concluded that there was no evidence of carcinogenicity in rodents administered THPS (US NTP, 1987).

The International Agency for Research on Cancer (IARC) evaluated the US NTP carcinogenicity studies in rodents and the in vitro and in vivo mutagenicity studies of tetrakis (hydroxymethyl) phosphonium salts. The IARC concluded that tetrakis (hydroxymethyl) phosphonium salts should be classified as a Group 3 carcinogen (Not classifiable as to carcinogenicity to humans) (IARC, 1999).

Reproductive and Developmental Toxicity

No data are available on the effect of THPS on the reproductive system in humans or animals. THPS is not considered a developmental toxicant.

In a developmental toxicity study conducted in accordance with OECD TG 414, New Zealand White rabbits were administered 75 % THPS solution by gavage at 0, 6, 18, or 60 mg/kg bw/day from gestation day (GD) 7–19. At the highest dose, decreased bodyweight gain of the dams was reported, indicating maternal toxicity. Increased incidence of foetal eye malformations (42/120) and hydrocephaly, or limb/phalangeal reduction defects were observed at the highest dose. No adverse effects were observed at the other doses (Barker, 1991a). No further study details were provided to reliably determine whether the developmental effects observed can be directly attributed to the chemical. The NOAEL for THPS maternal toxicity is 13.5 mg/kg bw/day. No foetal effects were observed in the absence of maternal toxicity. The relevance of these observations to developmental toxicity cannot be established due to the limited information provided.

In another study, Charles River CD rats were administered 75 % THPS solution at doses of 0, 15, 30, or 60 mg/kg bw/day from GD 6–15, by gavage. At the highest dose, decreased bodyweight gain of the dams was observed from GD 12 until the end of treatment. Incidence of foetuses with extra thoracic and/or lumbar ribs was increased at the highest dose (Barker, 1991b). The NOAEL for THPS maternal toxicity was 22.5 mg/kg bw/day. No foetal effects were observed in the absence of maternal toxicity.

Based on the limited reporting of the studies, it could not be reliably determined whether the developmental effects of THPS are attributable to the direct effect of the chemical or secondary to maternal toxicity.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include acute toxicity from oral exposure, severe eye irritation and skin sensitisation.

The chemical is slightly irritating to skin and might also cause harmful effects following repeated oral exposure.

Public Risk Characterisation

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

Occupational Risk Characterisation

During product formulation, dermal and ocular exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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 health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure to the chemical 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 appropriate controls.

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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation.

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)	Toxic if swallowed - Cat. 3 (H301)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Harmful: Danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)	May cause damage to organs through prolonged or repeated exposure through the oral route - 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 consumers

Products containing the chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from 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 which may 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;
- 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 assist with meeting 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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