2,5,8,11-Tetraoxadodecane: Human health tier II assessment

21 April 2016

CAS Number: 112-49-2

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	dimethoxytriethylene glycol triethylene glycol, dimethyl ether triglyme 1,2-bis(2-methoxyethoxy)ethane
Structural Formula	
Molecular Formula	C8H18O4
Molecular Weight (g/mol)	178.23
Appearance and Odour (where available)	Colourless liquid with ethereal odour
SMILES	C(COCCOCCOC)OC

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database; and
- various international assessments (ECHA, 2012; NICNASa; NICNASb).

The chemical has reported site-limited uses, including:

- in industrial solvents;
- in lubricants; and
- as an additive.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Appendix B, Part 3 'Substances considered not to require control by scheduling' (SUSMP, 2016).

International

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

- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products;
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain; and
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- R61 Repr. Cat.2; (Developmental toxicity)
- R62 Repr. Cat.3; (Reproductive toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard has been identified (Galleria Chemica):

An exposure limit of 36 mg/m^3 (5 ppm) short-term exposure limit in the USA (California).

Health Hazard Information

The chemical 2,5,8,11-tetraoxadodecane (CAS No. 112-49-2), also known as triethylene glycol dimethyl ether or ‘triglyme’ is used as a solvent and lubricant in industrial settings. The primary human health concerns associated with exposure to the chemical relate to its potential to cause harm to the unborn child and impair fertility in adults.

Given the high structural similarity between triglyme and diglyme (bis (2-methoxyethyl) ether) (CAS No. 111-96-6), data may be read-across where unavailable for the test chemical. The chemicals possess the same functional groups but differ by one ethylene group (ECHA, 2012). Diglyme has already been assessed by NICNAS under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNASa). Another structural analogue, glyme (CAS No. 110-71-4), has also been assessed under the IMAP framework (NICNASb) and may also be used as a read-across analogue for endpoints where data are lacking for triglyme.

The chemical is listed on the candidate list of substances of very high concern (SVHC). The Belgian Competent Authority has submitted an Annex XV report proposing to identify the substance as a category 1a or 1b Carcinogenic, mutagenic or toxic to reproduction (CMR), persistent bioaccumulative and toxic (PBT), very persistent very bioaccumulative (vPvB) or a substance of an equivalent level of concern (ECHA, 2012).

Toxicokinetics

There are no reported studies on triglyme. The following studies were conducted using diglyme.

The metabolism of diglyme has been studied in Sprague Dawley rats. Animals (n=five) received a single radiolabelled dose of the chemical at 5.1 mmol/kg bodyweight (bw) with urine collected and analysed six, 12, 24, 48, 72 and 96 hours following administration. The following metabolites were identified in the urine of rats in descending order of abundance: (2 -methoxyethoxy)acetic acid (MEAA), methoxyacetic acid (MAA), 2 -(2 -methoxyethoxy)ethanol (MEE), the precursor of MEAA; 2 -methoxyethanol (2ME), the precursor of MAA; N-(methoxyacetyl)glycine and diglycolic acid (DGA). Unchanged diglyme, representing 1.8 % of the administered dose, was excreted within 24 hours.

In a parallel study, radiolabelled diglyme was incubated with freshly prepared hepatocytes to assess in vitro metabolism of the test chemical. Exposure to 100 µM diglyme for 48 hours resulted in no significant signs of cytotoxicity. Five metabolites (MEAA, MME, MAA, DGA, 2ME) and the unmetabolised test chemical were identified in media recovered following incubation for 48

hours. MEAA was by far the most predominant metabolite in both the in vitro and in vivo system. Similar metabolic reactions with triglyme would lead to the same metabolites, as well as methoxyethoxyethoxyethanol and methoxyethoxyethoxyacetic acid.

Owing to the close structural similarity of triglyme and diglyme, similar skin penetration behaviour is also expected. As the molecular weight of triglyme (178.23 g/mol) is higher than that of diglyme (134.18 g/mol), the substance is expected to be absorbed by the skin at a lower rate compared with diglyme.

Glycol ethers are typically readily distributed throughout the body and eliminated through the urine (ECETOC, 2005).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in Wistar rats ranged from 5390–5877 mg/kg bw.

Triglyme was assessed for acute oral toxicity in a study conducted similarly to the Organisation of Economic Co-operation and Development (OECD) test guideline (TG) 401 (acute oral toxicity). Female Wistar rats (ten/dose group) were administered a single dose of the test chemical at 4000, 5000 or 6300 mg/kg bw by oral gavage. There were no control animals included in this study. Mortalities were 0/10, 4/10 and 8/10 for the groups which received 4000, 5000 and 6300 mg/kg bw, respectively. Clinical signs observed within a 14-day period in some animals including passivity, torpidness, deep anaesthesia, ataxia, abnormal positioning and posturing. Gross pathological examination of deceased animals revealed blood-filled lungs, blood present in the urinary bladders and liver surface discolouration. On the basis of these findings, an oral LD50 of 5390 mg/kg bw was determined (REACH).

In another acute oral toxicity study conducted similarly to OECD TG 401, triglyme was administered to Wistar rats. Animals (ten/dose group) were administered a single dose of the test chemical via oral gavage at 2500, 4000, 5000, 6300, 8000, 10000 and 15000 mg/kg bw. Mortalities for these groups were 0/10, 0/10, 1/10, 7/10, 10/10, 10/10 and 10/10, respectively. There were no control animals in this study. Animals died within 1–3 days of administration. Clinical signs observed within a 14-day period included disturbance of equilibrium, laboured breathing, anaesthesia-like signs and abnormal posturing. No macroscopic findings were reported in deceased animals. On the basis of these findings, an oral LD50 of 5877 mg/kg bw was determined (REACH).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats is >6900 mg/kg bw.

A study was conducted similarly to OECD TG 402 (acute dermal toxicity) to assess the potential for triglyme to cause dermal acute toxicity in male Wistar rats. Animals (two/dose) were administered the test chemical at 1.7, 3.5 or 6.9 g/kg bw under non-occlusive conditions. No animals died during the study; therefore, a dermal LD50 of >6900 mg/kg bw in male rats was determined (REACH).

Inhalation

Based on diglyme study data, the chemical is expected to have low acute inhalational toxicity.

Diglyme was assessed in an inhalation toxicity study according to OECD TG 403 (acute inhalation toxicity). Male and female Wistar rats (six animals/sex) were exposed to the aerosolised chemical at a concentration of 11.1 mg/L for a period of seven hours (nose-only system). No mortalities occurred during the study. No irreversible clinical signs were noted and no macroscopic lesions were observed upon dissection of animals. On the basis of this study, a median lethal concentration (LC50) of >11.1 mg/L was determined for diglyme (REACH).

Corrosion / Irritation

Skin Irritation

The chemical did not produce signs of skin irritation in a study that was performed in accordance with OECD TG 404 (acute dermal irritation/corrosion).

In a study conducted similarly to OECD TG 404, triglyme was assessed for its potential to cause dermal irritation/corrosion. Six albino Russian rabbits were administered 500 µL of pure test substance to 2.5 cm^2 shaved portions of skin under occlusive conditions. Animals were exposed for a period of 24 hours and assessed for signs of irritation at 24, 48 and 72 hours post-application. No signs of irritation were noted in any animal, at any time point. On the basis of this study, the chemical was not considered to be a skin irritant (REACH).

Eye Irritation

The chemical was reported to slightly irritate the eyes. The effects do not warrant hazard classification.

An ocular irritation study was conducted similarly to OECD TG 405 (acute eye irritation/corrosion) to assess the potential for triglyme to cause ocular irritation. Albino Russian rabbits had 0.1 mL of pure test substance instilled into one eye. Animals were split into two groups, one containing five animals that had their eyes rinsed five minutes after application and one containing three animals that had their eyes washed 24 hours after application. The eyes were examined one, two, three, seven, 14 and 21 days following washing. Minimal conjunctival irritation was observed in some animals in the 24 hour rinse group. On the basis of these findings, the chemical was determined to be slightly irritating (REACH).

Sensitisation

Skin Sensitisation

The chemical is not a skin sensitiser.

To assess the potential for triglyme to cause skin sensitisation, a study utilising the local lymph node assay protocol was conducted according to OECD TG 429. Female CBA mice (four/dose) were treated topically on the dorsum of each ear for three consecutive days with the test chemical at concentrations of 25, 50, and 100 % in vehicle. Five days after the first application, animals were injected intravenously into the tail vein with radiolabelled thymidine. Animals were sacrificed and draining lymph node cells were assessed for incorporation of thymidine. In this study stimulation index (SI) values of 0.73, 1.03 and 0.69 were determined at concentrations of 25, 50 and 100 %, respectively. No ‘estimated concentration required to produce a three-fold increase in lymphocyte proliferation’ (EC3) was able to be calculated as none of the concentrations tested resulted in an SI value greater than three. On the basis of this study, the test chemical was not considered to be a skin sensitiser (REACH).

Repeated Dose Toxicity

Oral

Considering the No Observed Adverse Effect Level (NOAEL) available from a 28-day rat study (250 mg/kg bw/day), repeated oral exposure to the chemical is not considered to cause serious damage to health.

A study was conducted similarly to OECD TG 407 (repeated dose 28-day oral toxicity in rodents) to assess the effects of repeated dosing with triglyme. Rats (WISKf) of both sexes (five/sex/dose) were administered the test material at 0, 62.5, 250 or 1000 mg/kg bw/day, once daily for 29 days, by oral gavage. There were no mortalities during the study. Male and female

animals in the highest dose group showed reduced thymus weights and males showed reduced testes weights and impaired spermatogenesis. On the basis of these findings, a NOAEL of 250 mg/kg bw/day was determined (REACH).

A 14-day study was conducted in compliance with good laboratory practice to assess the effect of repeated dosing with triglyme. Male and female CD-1 mice (eight/sex/dose) were administered the chemical in drinking water at 0, 0.25, 0.5, 1.0, 2.5 or 5 % for 14 days. Dosed water was provided to animals ad libitum. No dose conversions were provided for this study. Two males in the 0.5 % group exhibited dehydration, piloerection, and/or lethargy. Six males in the 2.5 % group exhibited these signs, as well as ptosis. These signs were observed in seven males and all females in the 5.0 % group in addition to tremors. No clinical signs were observed in either sex in the 0.25 and 1.0 % dose groups. During the treatment period, two males in the 0.5 % group, six males in the 2.5 % group and five males and two females in the 5.0 % dose group, died. On the basis of these findings, the No Observed Effect Level (NOEL) is considered to be 0.25 % in drinking water (REACH).

Dermal

No data are available.

Inhalation

No repeat dose inhalation data are available for triglyme. While data are available for the analogue diglyme, the dominant effects seen in this study were in the reproductive system and haematopoietic system (NICNASa). The effects are considered likely to be due to metabolites including MAA. As data are not available to compare metabolism of triglyme with that of diglyme, conclusions cannot be made using this read-across data.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro

An in vitro study was conducted similarly to OECD TG 471 (bacterial reverse mutation assay) to assess the potential for triglyme to cause genotoxicity. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were incubated with the chemical at concentrations ranging from 4–10,000 µg/plate, in a bacterial reverse mutation assay (Ames test), in the presence and absence of S9 activation. No bacterial cytotoxicity was observed at any concentration and no significant increases in the number of revertant colonies were observed at any of the concentrations tested, either in the absence or presence of S9 activation. Therefore, the test substance was not considered to be genotoxic under these conditions (REACH).

In vivo

Glyme (CAS No. 110-71-4) is a structurally similar chemical to triglyme with the same functional groups and is thought to be metabolised in a similar fashion to form some common metabolites. The in vivo genotoxicity study summarised below may provide some insight into the genotoxicity of triglyme in vivo.

An in vivo chromosome aberration study was conducted similarly to OECD TG 475 (mammalian bone marrow chromosome aberration test). Male and female Han:Chinese hamsters (five/sex/dose group) were administered glyme orally at 2000 mg/kg bw. Animals were euthanised six, 26 and 50 hours after dosing and bone marrow was harvested. Glyme did not produce any detectable increase in the number of chromosomal aberrations in bone marrow cells indicating that the chemical was not genotoxic under these conditions (REACH).

Carcinogenicity

No data are available for triglyme. A range of related compounds, including glyme, diglyme and related monomethyl esters (cellosolves) are not considered carcinogens (NICNASa; NICNASb).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 2 substance toxic to reproduction—with the risk phrase ‘May cause harm to the unborn child’ (T; R61) and Category 3 substance toxic to reproduction—with the risk phrase ‘Possible risk of impaired fertility’ (T; R62) in the HSIS (Safe Work Australia). The available data support these classifications.

A well-documented study was conducted similarly to OECD TG 414 (prenatal development toxicity). Pregnant New Zealand White rabbits were dosed with triglyme on gestational days (GD) 6-19 at 0, 75, 125, 175 or 250 mg/kg bw/day by oral gavage. Doses were selected following preliminary range-finding experiments. Mortalities for pregnant rabbits exposed to the test chemical were 0, 2, 0, 0 and 0 for the 0, 75, 125, 175 or 250 mg/kg bw/day groups, respectively. The two deaths were suspected to be caused by experimental error; however, this could not be conclusively confirmed. Maternal body weights did not differ significantly among treatment groups. On GD 19, maternal body weight was significantly reduced in the 175 and 250 mg/kg bw/day groups. Gravid uterine weights exhibited a dose-related decreasing trend. Absolute maternal liver weight increased in a dose-related manner. The number of does with entirely resorbed litters and no live foetuses was 1, 1, 2, 2, and 7 for the 0, 75, 125, 175 and 250 mg/kg bw/day groups, respectively. There were also significant dose-dependent increases in the percentage of adversely affected implants, pre-implantation loss of foetuses, non-live implants and foetal resorptions. The percentage of litters with adversely affected implants exhibited an increasing trend with both the 175 and 250 mg/kg bw/day dose groups significantly above controls. The percent of dead foetuses per litter and the percentage of litters with resorptions or with dead foetuses were not significantly affected by treatment with triglyme. At doses of 175 and 250 mg/kg bw/day, the test chemical caused a significant increase in the incidence of malformed foetuses per litter, and in the incidence of litters with malformed foetuses. Malformations included missing toenails in foetuses of normal size with no digital abnormalities, abnormally small spleens, and hydronephrosis. On the basis of these findings, a NOEL of 125 mg/kg bw/day was determined for maternal toxicity and a NOEL of 75 mg/kg bw/day was determined for developmental toxicity (REACH).

In another study conducted similar to OECD TG 414, CD-1 mice (28-32 animals/group) were dosed with the chemical at 0, 250, 500 or 1000 mg/kg bw/day, on GD days 6-15. At sacrifice on GD 17, pregnant females were evaluated for clinical status and gestational outcome; each live foetus was examined for external, visceral, and skeletal malformations. No maternal mortalities occurred during the study. Relative maternal liver weight, but not absolute liver weight, was increased significantly at 500 and 1000 mg/kg bw/day. The average foetal body weight per litter was significantly reduced at doses of 500 mg/kg bw/day and above. The percentage of malformed live foetuses per litter and percentage of litters with one or more malformed foetuses were both significantly increased at 1000 mg/kg bw/day dose. On the basis of these changes, a NOAEL of 250 mg/kg bw/day was determined for maternal toxicity and a NOAEL for developmental toxicity was determined to be 250 mg/kg bw/day under the conditions of this study (REACH).

Oral repeat dose toxicity studies showed effects of the chemical on the male reproductive system with the likely effect being impaired male fertility (see **Repeat dose toxicity**).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity and developmental toxicity).

Public Risk Characterisation

Given the site-limited 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

During product formulation, dermal, ocular and inhalation exposure may 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 chemicals 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 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.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Given the uses identified for this chemical, the public are unlikely to be exposed. However, if information becomes available indicating that its use pattern has changed, further risk management may be required to protect the general public.

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]
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage fertility or the unborn child - Cat. 1B (H360)
Other Health Effects	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility or the unborn child - Cat. 2 (H361)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, 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;
- 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 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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Last update 21 April 2016