1,3,5-Trioxane: Human health tier II assessment

05 February 2016

CAS Number: 110-88-3

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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.

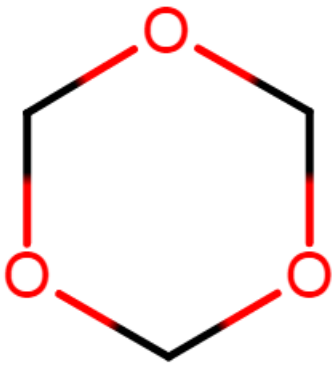
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	trioxymethylene s-trioxane trioxane trioxin
Structural Formula	
Molecular Formula	C3H6O3
Molecular Weight (g/mol)	90.08
Appearance and Odour (where available)	crystalline white solid with a chloroform-like odour
SMILES	C1OCOCO1

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 and Authorisation of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database; and
- the National Toxicology Program (NTP) assessment report (NTP, 1999).

The chemical has reported commercial uses including:

- in construction materials; and
- in non-luminous, odourless fuel.

The chemical has reported site-limited uses including:

- as a chemical intermediate in organic synthesis (mainly in the production of acetyl resins) and in the manufacture of artificial horn, ivory and synthetic resins; and
- in the manufacture of organic chemicals and plastics products (e.g. highly crystallise thermoplastics).

The chemical has reported non-industrial uses in disinfectants (e.g. medical disinfectant) and as an active ingredient in some contraceptive creams.

Restrictions

Australian

No known restrictions have been identified.

International

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

- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- Chile list of substances which must not form part of the composition of cosmetic products;
- China list of banned substances for use in cosmetics;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

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):

Xi; R37 (irritation)

Repro. Cat. 3; R63 (reproductive toxicity)

Exposure Standards

Australian

No specific exposure standards are available for the chemical.

The chemical is a cyclic trimer of formaldehyde, and decomposes to formaldehyde under acidic conditions or on heating. Formaldehyde has an exposure standard of 1.2 mg/m^3 (1 ppm) time weighted average (TWA) and 2.5 mg/m^3 (2 ppm) short-term exposure limit (STEL) (HSIS).

International

The following exposure standard is identified (Galleria Chemica).

An exposure limit of 15 mg/m^3 TWA and 75 mg/m^3 STEL in Poland.

Health Hazard Information

The chemical 1,3,5-trioxane, also known as trioxymethylene and trioxane (with molecular formula $C_3H_6O_3$) is a stable cyclic trimer of formaldehyde, and one of the three trioxane isomers. It is manufactured by distilling formaldehyde with an acid catalyst, with solvent extraction (NTP, 1999). The chemical is highly water-soluble and decomposes into three molecules of formaldehyde in acidic conditions. The inhalation route is expected to be the primary route of exposure and, when heated, the chemical will be available as formaldehyde vapour (NTP, 1999; REACH). Therefore the hazard characterisation of the chemical by the inhalation route includes consideration of animal studies and human observations on formaldehyde (CAS No. 50-00-0) (NICNAS, 2006).

Toxicokinetics

The chemical is metabolised into formaldehyde. In a study of its distribution, excretion and metabolism, the chemical was distributed mainly to the liver and to a lesser extent to the fat and brain tissues, and excreted mainly as exhaled CO_2. As the chemical is eliminated rapidly, it is not expected to biaccumulate (NTP, 1999).

Absorption & Distribution:

Single application by intraperitoneal injection (i.p.) of 40 or 400 mg/kg bw in rats resulted in the highest concentration of the chemical in the liver and low concentrations in fat tissue, sciatic nerve and brain at 40 mg/kg. At the 400 mg/kg bw dose, the highest concentration was found in plasma, liver and kidneys with low concentrations found in fat tissue and brain. A rapid decline in concentrations of the chemical was noted in all tissues. The total amount of the absorbed chemical in tissues and blood after 72 hours post-application was not significant and constituted about 1.2 % of the initial dose for animals treated with 40 mg/kg bw and 1.5 % of the initial dose for animals treated with 400 mg/kg bw (REACH).

Metabolism:

The chemical was reported to undergo metabolic transformation (enzymatic transformation) to formaldehyde, with carbon dioxide and water being the final products (REACH).

Excretion:

The main route of elimination was through exhaled air (CO_2), followed by excretion through the urine and faeces. At the 40 mg/kg dose (72-hours post-administration) and 400 mg/kg dose (12-hours post-administration), the total excretion of the chemical was reported to be approximately 89.5 % and 80 %, respectively (REACH).

Acute Toxicity

Oral

The chemical has low acute oral toxicity based on results from non-guideline animal studies in rats following oral exposure. The median lethal dose (LD50) was reported to be >2000 mg/kg bw (8500 mg/kg bw in male Wistar rats and 5000 mg/kg bw in rats of unspecified sex and strain (NTP, 1999; REACH)).

Dermal

The chemical has low acute dermal toxicity based on results from non-guideline animal studies in male rabbits (unspecified strain) following dermal exposure. The median lethal dose (LD50) was reported to be >2000 mg/kg bw (>3980 mg/kg bw, 10000 mg/kg bw and >15000 mg/kg bw, respectively). In one of the studies, reversible effects of very slight to moderate erythema were reported within a 14-day observation period (NTP, 1999; REACH).

Inhalation

The chemical has low acute inhalation toxicity based on results from non-guideline animal studies in Sprague Dawley (SD) and Wistar rats following inhalation exposure. The median lethal concentrations (LC50s) were reported to be >39.2 mg/L and >26 mg/L, respectively (REACH).

Formaldehyde is reported to be moderately acutely toxic in rats and mice by inhalation exposure (NICNAS, 2006).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). There are sufficient data available from animal studies (refer to **Repeat Dose Toxicity: Inhalation)** and human observations to support this classification (refer to **Irritation: Observation in Humans** section).

Skin Irritation

The chemical is not considered to be irritating to the skin.

In two skin irritation studies (OECD TG 404) using New Zealand White rabbits, the chemical was non-irritating to the skin. No reactions indicative of skin irritation were reported in the studies (REACH).

Eye Irritation

The chemical is not considered to be irritating to the eyes.

Two eye irritation studies (OECD TG 405) conducted using the chemical in New Zealand and Vienna White rabbits indicated that the chemical was non-irritating to the eyes (mean iris, conjunctival, redness and chemosis scores of 0.11, 1.66 and 0.66 at 24, 48, and 72-hours examination but reversible by 72 hours after instillation in one study). In the second study, only irritation resulting from mechanical damage (no treatment-related adverse effects) was reported (REACH).

Observation in humans

In humans, breathing formaldehyde vapour can result in sensory irritation (eye, nose and respiratory tract irritation) at levels in air of >0.5 ppm. Reported effects include irritation of nerves in the eyes and nose, which may cause burning, stinging or itching sensations, a sore throat, teary eyes, blocked sinuses, runny nose, and sneezing (NICNAS, 2006).

Sensitisation

Skin Sensitisation

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

Negative results for skin sensitisation were reported in a guinea pig maximisation test (GPMT) conducted in accordance with OECD TG 406. Female Pirbright-Hartley guinea pigs (four/dose) were administered the chemical at 5 % for intradermal induction and at 50 % for epicutaneous injection respectively. Animals were then challenged 14 days-post percutaneous exposure at 50 % concentration and then re-challenged seven days after the first challenge exposure at 50 % concentration. Skin irritation (erythema and oedema) were reported during the induction phase but no reactions indicative of sensitisation were reported at challenge (REACH). Formaldehyde solutions are strongly sensitising to skin (NICNAS, 2006).

Repeated Dose Toxicity

Oral

Based on the available information, hazard classification for repeated dose oral toxicity is not recommended.

In a 28-day repeated dose oral study (OECD TG 407),Wistar rats (five/sex/dose) were dosed at 40, 200 or 1000 mg/kg bw/day of the chemical. At 1000 mg/kg bw/day, a significant decrease in leukocyte count, and significant decrease in bilirubin, indicative of hepatic damage, were reported. The no observed adverse effect level (NOAEL) and the lowest observed adverse effect (LOAEL) were determined to be 200 mg/kg bw/day and 1000 mg/kg bw/day, respectively (REACH).

In a 90-day repeated dose oral toxicity study (OECD TG 408), Wistar rats were (10/sex/dose) administered by oral gavage at doses of 0, 30, 100 or 300 mg/kg bw/day of the chemical. Recovery groups (five/sex/dose) were dosed at 0 and 300 mg/kg bw/day. A non-statistically significant decrease in spleen weight in some males at the highest dose, compared with controls, was reported. This effect was reversible following the four weeks recovery period. The NOAEL was reported to be 300 mg/kg bw/day (REACH).

Dermal

No data are available for this chemical.

Inhalation

Based on the available information, hazard classification for repeated dose inhalation toxicity is not recommended. However, classification for respiratory irritation is warranted (refer to **Irritation: Respiratory** section).

A 14-day repeated dose inhalation study reported treatment-related systemic effects when SD rats (five/sex/dose) were exposed (as whole-body vapour) to the chemical at concentrations of 100, 1000 and 5000 ppm (approximately 380, 3620 or 18180 mg/m^3), six hours/day, five days/week for two weeks. Reduced body and organ weights were reported in both sexes at all doses (but only statistically significant at the highest dose) with changes in haematological and clinical chemistry parameters compared with controls. At the highest dose, central nervous system impairments (reduced righting reflex and grip strength as well as persistent pupillary constriction) were also noted. Histopathology examinations of animals exposed to mid- and high doses indicated adverse effects in the upper respiratory tract (squamous metaplasia and necrosis of the nasal cavity). Treatment-related local effects including increased secretory responses (lacrimation and mucoid nasal discharge) were also reported at all doses for both sexes. The no observed adverse effect concentration (NOAEC) for systemic toxicity was determined to be 3620 mg/m^3 based on reduced body weight, and effects on the haematopoietic system and variations on clinical chemistry parameters in the highest dose group. The lowest observed adverse effect concentration (LOEAC) for local toxicity was reported to be <380 mg/m^3 based on effects of the upper respiratory tract at all doses (REACH).

In male Wistar rats, chronic inhalation exposures (up 500 mg/m^3) to the chemical caused pulmonary irritation and central nervous system impairment (NTP, 1999; REACH).

Formaldehyde is reported to have low toxicity following repeated inhalation exposure in rats, mice, hamsters and monkeys. However, irritation of the nasal tract was indicated in rat studies. Dose-dependent effects reported included alterations in mucociliary clearance, cell proliferation and histopathological changes to the nasal epithelium. The no observed adverse effect level (NOAEL) for local effects was reported to be 1.2 mg/m^3 (1 ppm) (NICNAS, 2006).

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic.

Several in vitro assays using the chemical gave negative results (NTP, 1999; REACH) in the following studies:

- bacterial mutation assays (various *Salmonella typhimurium* strains) with and without metabolic activation at doses of up to 5000 µg/plate;
- a mammalian cell gene mutation assay in Chinese hamster lung fibroblasts (V79) cells with and without metabolic activation at doses of up to 900 µg/mL;
- chromosomal aberrations in Chinese hamster lung fibroblasts (V79) cells with and without metabolic activation at doses of up to 909 µg/mL.

The chemical also gave negative results in the following in vivo studies (NTP, 1999; REACH):

- unscheduled DNA synthesis test in Wistar rat mammalian liver cells at doses of up to 2000 mg/kg;
- mammalian erythrocyte micronucleus test in Balb/c mouse bone marrow cells at doses of 2125 or 4250 mg/kg; and
- rodent dominant lethal tests in Wistar rats at doses of 2500 mg/m^3 (0.25 mg/L) and at doses up to 1700 mg/kg.

Formaldehyde is reported to have weak genotoxic potential (NICNAS, 2006).

Carcinogenicity

Based on the limited animal data, the chemical is not considered likely to be carcinogenic. Furthermore, the chemical presented no alerts for mutagenicity or carcinogenicity based on its molecular structure as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.3.

In a non-guideline study, rats of unspecified strain (30/sex/dose) were administered with 0, 1 % or 5 % of the chemical orally (equivalent to 0, 200–310 or 870–1400 mg/kg bw/day, males–females), daily for 104 weeks. No statistically significant difference in the incidence of tumours was reported. By the second year of the study, 60 % mortality was reported in all groups (non-dose

response relationship) due to lung infection. The authors of the study considered the lung effects as non-treatment related as similar findings were observed in surviving animals at termination of the study. Non-neoplastic effects were seen in the lungs, liver, kidney, spleen and heart. Neoplastic effects including skin tumours of lower binding layer, small gall bladder canals and spleen hyperplasia, ovarian and uterine tumours were reported. However, these effects were considered isolated occurrences, or were not statistically significantly different when compared to controls.

Formaldehyde is reported to cause nasal cancers (squamous cell carcinomas of the nasal cavity) in rats (but not in mice or hamsters) through the inhalation route only, at levels not found in the majority of workplaces (concentrations >6 ppm). Human epidemiological data indicate a link between nasopharyngeal tumours and formaldehyde exposure. Formaldehyde is classified as 'probably carcinogenic to humans' (NICNAS, 2006).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrase 'Possible risk of harm to the unborn child' (Xn; R63) in HSIS (Safe Work Australia). Neurodevelopmental impairment observed in one study supports this classification.

Reproductive toxicity

In a non-guideline reproductive study, male Wistar rats exposed by inhalation to the chemical over 12 months showed no treatment-related adverse effects on reproductive parameters at doses up to 2500 mg/m^3 (equivalent to 0.25 mg/L). No histopathological changes in the testes were reported. The developmental effects reported were secondary effects due to maternal toxicity which occurred at the lowest dose tested 100 mg/kg bw/day (REACH).

Developmental toxicity

In a developmental toxicity study (OECD TG 414), Wistar rats were orally exposed to the chemical in drinking water at daily doses of 0, 100, 315 or 1000 mg/kg bw/day on gestation days (GD) 7–20. At the mid- and high dose groups, signs of foetal retardation (decreased foetal body weight, crown-rump length and placental weights, and aplasia of the tail), significant congenital skeletal malformations (aplasia of sacral vertebral arch, sacral vertebral centres and 1st and 2nd caudal vertebral centre) and maternal toxicity (reduction in mean corrected body weight gain) were reported.

In a guideline study (OECD TG 414 with study deviations),Wistar rats were orally administered 190, 580 or 1160 mg/kg bw/day of the chemical on GD 2–20. Treatment-related adverse effects included impaired post-natal neurobehavioural development in surviving pups of the low and mid-dose groups. Statistically significant animal mortality (92.3%) was reported at the high dose group. Maternal toxicity (reduced body weights and reduced litter sizes) was also observed at the high dose group. The NOAEL for developmental and maternal toxicity was reported to be 190 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (developmental toxicity) and local effects (respiratory irritation). If the chemical is heated, formaldehyde vapour will be of particular concern for toxicity (refer to **Occupational Risk Characterisation** section).

Public Risk Characterisation

Although the public could be exposed to the chemical through commercial uses, the chemical is mainly used as an intermediate (refer to **Import, manufacture & use** section). Public exposure is considered to be low and the chemical can be managed through appropriate labelling, thus the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These can include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations can 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. Furthermore, if the chemical is heated, it is readily available as formaldehyde vapour. Labelling for formaldehyde formulations is controlled by the *Poisons Standard - Schedule 2 and 6* (SUSMP, 2015).

Given the critical systemic long-term health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise inhalation exposure to the chemical are implemented. Appropriate precautions should also be taken to avoid inhaling vapours. 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

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

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]
Irritation / Corrosivity	Irritating to respiratory system (Xi; R37)*	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)*	Suspected of damaging the unborn child - Cat. 2 (H361d)

[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 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 which 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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