1,3-Dioxan-4-ol, 2,6-dimethyl-, acetate: Human health tier II assessment

25 November 2016

CAS Number: 828-00-2

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.

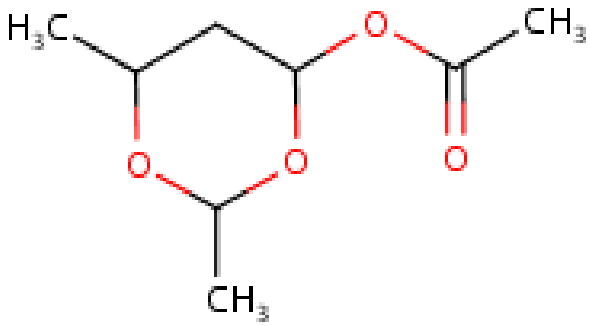
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,6-dimethyl-1,3-dioxan-4-ol acetate dimethoxane acetic acid, 2,6-dimethyl-m-dioxan-4-yl ester 2,4-dimethyl-6-acetoxy-1,3-dioxane acetomethoxane
Structural Formula	
Molecular Formula	C8H14O4
Molecular Weight (g/mol)	174.2
Appearance and Odour (where available)	Colourless to yellow fluid with a typical halide odour
SMILES	C(C)(=O)OC1CC(C)OC(C)O1

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: Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); International Agency for Research on Cancer (IARC); United States Environmental agency (US EPA); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical is a biocide used to preserve emulsions and water-based industrial processes. Use concentrations range from 0.01 % to 0.2 % (US EPA, 2010).

The chemical has reported commercial uses in:

- paints;

- coatings;
- water-based cutting oils;
- speciality textile chemical emulsion;
- pigment slurries;
- dyestuffs;
- fabric softeners;
- latex emulsions;
- sizings;
- adhesives;
- antistatic lubricants;
- spinning emulsions (at concentrations of 500–1500 mg/kg);
- inks;
- thickeners;
- gums;
- lignosulfate;
- distillation fuels;
- leather processing liquors; and
- fuel as an additive.

Although paints and coatings could have potential domestic applications the chemical is reported to be only used in industrial settings. In addition no uses were identified in US Household Products Database (HHPD).

The chemical has identified historical cosmetic use at up to 0.2 % (SCC, 1987; NTP, 1989). However the chemical is not reported as being used in cosmetic products in the US (Personal Care Products Council, 2011), not listed in the US Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and is prohibited in several countries (refer **Restrictions: International** section).

The chemical has reported non-industrial use, including:

- as a biocide in pesticides.

Restrictions

Australian

No known restrictions have been identified.

International

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

- 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;
- Canada Cosmetic Ingredient Hotlist - List of ingredients that are prohibited for use in cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (82/368/EEC);
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Chile list of substances which must not form part of the composition of cosmetic products; and

- China list of banned substances for use in cosmetics.

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

No specific international exposure standards are available.

Health Hazard Information

The majority of studies were conducted on commercial grade dimethoxane which contains 80–95 % of the chemical. Detected impurities include acetaldehyde (CAS No. 75-07-02), 3-hydroxybutyraldehyde (CAS No. 107-89-1), and 2-butenal (CAS No. 123-73-9) (NTP, 1989).

The chemical is expected to undergo hydrolysis in biological systems (refer **Toxicokinetics** section). Data for the metabolites has been included as supporting data for chronic systemic toxicity endpoints.

Toxicokinetics

The chemical hydrolyses in water to form acetic acid and a transient intermediate, dioxinol (1,3-Dioxan-4-ol, 2,6-dimethyl-, CAS No. 4740-77-6). The dioxinol then breaks down into acetaldehyde (CAS No. 75-07-02) and 3-hydroxybutyraldehyde (CAS No. 107-89-1). Equimolar quantities of 3-hydroxybutyraldehyde, acetaldehyde and acetic acid are produced during this hydrolysis. The 3-hydroxybutyraldehyde produced exists in equilibrium with 2-butenal (CAS No. 123-73-9) (NIOSH, 1982; US EPA, 1997).

The chemical is highly unstable in water with over 50 % of the chemical hydrolysed in 2 hours. The breakdown into acetic acid and the intermediate dioxinol is completed in 14 hours (US EPA, 2010; NIOSH 1982).

No detectable amount of dimethoxane was found in the urine of rats and mice 24 or 48 hours after a single administration of the chemical either by oral gavage or dermally (NTP, 1989). In another study, no detectable amount of dimethoxane was found in the blood of male mice or rats 15 or 30 minutes or 1, 2, or 4 hours following oral or dermal exposure to 2800 mg/kg bw (rats) or 954 mg/kg bw (mice).

The metabolite, 2-butenal, is rapidly absorbed and can be further metabolised in the liver, with 60–78 % of it being excreted in urine and breath within 12 hours of dosing and this increased to 82–86 % after 72 hours (NICNASa).

Acute Toxicity

Oral

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

An oral median lethal dose (LD50) value of 1930 mg/kg bw was reported in rats (NTP, 1989);

In a single administration study, Fischer (F344/N) rats and B6C3F1 mice were dosed with 175, 350, 700, 1400 and 2800 mg/kg dimethoxane in corn oil by gavage. All male and 4/5 female rats that received 2800 mg/kg dimethoxane died before the end of the studies. Four of five males and 4/5 female mice that received 2800 mg/kg dimethoxane died within 24 hours. No chemical-related clinical signs were seen in the mice (NTP, 1989). The LD50s in these studies are <2800 mg/kg bw.

Using a commercial product composed of 87 % of the chemical, oral LD50 values of 2086 mg/kg bw and 3160 mg/kg bw were reported for male and female rats, respectively (US EPA, 1996; Givaudan-Roure).

Dermal

The chemical has low acute dermal toxicity based on the available data.

The dermal LD50 in rats was >2000 mg/kg bw (US EPA, 1996). No signs of systemic toxicity or severe dermal effects were observed. Macroscopic postmortem evaluations revealed no significant changes (Givaudan-Roure). No other details from this study are available.

No mortality occurred in a study in which rats and mice were dermally exposed to a single dose of the chemical (2800 mg/kg bw—rats, 920–954 mg/kg bw—mice) (NTP, 1989).

Inhalation

The chemical has low to moderate acute inhalation toxicity based on the available data. Given that 50 % mortality was not observed at the maximum attainable concentration classification is not considered warranted.

The median lethal concentration (LC50) in rats is >4 mg/L (US EPA 1996). Sprague Dawley (SD) caesarean-derived (CD) rats (5/sex/group) were exposed to the chemical as a vapour/aerosol for four hours. The mean analytical exposure concentrations were 4.0 and 3.1 mg/L, resulting in mortalities of 40 % and 0 %, respectively. The 4.0 mg/L was considered a maximum attainable exposure level. Signs of toxicity during exposure included respiratory and secretory irritation. During the 14-day post-exposure observation period, similar responses persisted during the first week after exposure and then generally abated. Macroscopic postmortem evaluations revealed no significant changes (Givaudan-Roure).

Corrosion / Irritation

Respiratory Irritation

Reversible respiratory irritant effects were observed in an acute inhalation toxicity study in rats (refer **Acute toxicity** section).

Skin Irritation

Based on the limited data available the chemical is considered to be a slight skin irritant. The severity of effects may increase with prolonged exposure.

In a primary rabbit dermal irritation study, slight erythema, with irritation clearing in all but one animal by 48 hours was reported (US EPA, 1996). No other details from this study are available. In another report, repeated application of a 10 % solution of the chemical induced slight skin irritation in guinea pigs (SCC, 1987).

Epidermal hyperplasia, hyperkeratosis and sebaceous gland hyperplasia were observed in seven week dermal toxicity studies in rats and mice. Necrosis and ulceration were also observed in the mouse study (NTP, 1989).

Eye Irritation

Based on the limited data available the chemical is considered to be a slight to moderate eye irritant. Sufficient data to warrant classification are not available.

In a primary eye irritation study in rabbits, mild transient ocular irritation was observed (US EPA, 1996). The commercial product (neat) produced moderate irritation only in the conjunctivae. Effects had cleared on the fourth day of observation. A 1 % aqueous solution (of a commercial product) did not produce any irritation or injury during a seven day observation period (Givaudan-Roure).

In another study, 10 % was well tolerated in rabbit eyes, while higher concentrations produced moderate irritation of the conjunctivae (SCC, 1987).

Observation in humans

It has been reported that the chemical at 1 % does not to cause irritation in humans (SCC, 1987). No further details were available.

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser. Aqueous solutions of the chemical contain the hydrolysis products acetaldehyde and butenal—there is evidence that both these hydrolysis products are skin sensitisers (NICNASa; NICNASb). Hazard classification is recommended (refer **Recommendation** section).

The chemical was shown to be a strong sensitiser when tested in a guinea pig maximisation test. No other details on this study are available (US EPA, 1996; Givaudan-Roure; DOW).

QSAR

The chemical contains a structural alert for binding to proteins as indicated in the profiling functionality of the OECD Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (v.3.4). However, the chemical gave a negative prediction for skin sensitisation based on OASIS-TIMES (v.2.27.19). Predictions were within the applicability domain of the model.

Observation in humans

Limited human data are available. Allergic contact dermatitis was reported in a textile worker occupationally exposed to the chemical.

The chemical at a concentration of 1.25 % sensitised 50 out of 205 subjects in a Draize test (de Weck and Bundgaard, 2012).

Repeated insult patch tests (Shelanski & Shelanski protocol) with a 1 % solution of the chemical were applied to a panel of 52 subjects, producing no irritation or sensitisation reactions (TSCATS).

Repeated Dose Toxicity

Oral

The chemical is not considered to cause serious damage to health from repeated oral exposure. The toxic effects of dimethoxane appeared to be associated with the irritant responses at the primary site of chemical application, i.e., the stomach in the gavage studies and the skin in the dermal studies.

In a 13-week study, F344/N rats and B6C3F1 mice were treated with the chemical in corn oil by gavage at 0, 31, 62, 125, 250, or 500 mg/kg bw/day, 5 day/week. No compound-related deaths were noted in either species at any dose. Male rats appeared to be more responsive than female rats, while male and female mice were equally responsive to the forestomach toxicity of this chemical. Rats that received 500 mg/kg bw/day had lower (17 % for males and 5% for females) mean body weight than that of vehicle controls. The relative organ weights (kidney, brain, and lung) for male rats at 500 mg/kg bw/day were slightly greater than those for vehicle controls. The final mean body weights in mice were not affected by treatment. The relative kidney weights for dosed female mice were greater than those for vehicle controls and the relative liver weights for dosed male mice were lower than those for vehicle controls. Compound-related lesions were restricted to the forestomach in both species. Lesions consisted of acanthosis (hyperplasia of the squamous epithelium), with accumulation of keratin on the surface. Ulceration and inflammation of the forestomach were observed in rats dosed with 250 and 500 mg/kg bw/day. The incidence and severity of the acanthosis and hyperkeratosis increased with increasing doses of the chemical. Acanthosis and hyperkeratosis of the squamous epithelium were observed in male rats at doses ≥62 mg/kg bw/day, and in female rats at doses ≥250 mg/kg bw/day; and in male (4/10) and female (1/10) mice at 500 mg/kg bw/day (NTP, 1989).

In a 15-month study conducted to determine the dose for a carcinogenicity study, F344/N rats and B6C3F1 mice were treated with the chemical in corn oil by gavage 5 day/week for 66 week (rats) or 65 week (mice). Minimal diffuse acanthosis and hyperplasia of the forestomach were seen in 7/10 female rats at 250 mg/kg, 7/10 males at 125 mg/kg, and 1/9 male and 1/9 female vehicle controls. Acanthosis of the forestomach was seen in 7/10 male and 6/10 female mice at 500 mg/kg. Several adenomas and carcinomas were observed (see **Carcinogenicity** section). No compound-related effects were observed among the clinical chemical or haematologic values or for organ weights for rats or mice (NTP, 1989). Local effects in the forestomach were the main non-neoplastic effects seen in rats and mice in a 2-year carcinogenicity study (see **Carcinogenicity** section).

In a 16-day acute oral toxicity study, rats and mice received up to 2000 mg/kg bw/day dimethoxane in corn oil. All rats and one male mouse that received 2000 mg/kg died within one week. Body weights of rats and mice were similar to those of vehicle controls. Compound-related clinical signs were not seen in surviving rats. Haemorrhage and necrosis of the stomach were observed in rats in the 2000 mg/kg group which died before the end of the studies. Lesions of the forestomach, including inflammation, hyperplasia, hyperkeratosis, and ulceration, occurred in rats that received 250–2000 mg/kg bw/day. Mice that received 500–2000 mg/kg bw/day dimethoxane had lesions of the forestomach including erosion, ulceration, hyperplasia, and hyperkeratosis. Forestomach lesions were not seen at 125 or 250 mg/kg bw/day (NTP, 1989).

Dermal

The chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a dermal subchronic study, the chemical was applied to the skin of SD rats (for 6 hrs/day, 5 days/week for three months) at 0, 100, 300, or 1000 mg/kg bw/day. The chemical was applied for six hours after which the test site was cleaned with water. The effects seen were associated with the site of chemical application. Eschar formation and superficial necrosis were observed on one male and two females in the highest dose group. Systemic effects were also observed at 300 and 1000 mg/kg bw/day and included decreased body weight gain and hepatic lesions. The lesions consisted of minimal or slight necrosis, inflammation or haemorrhage. Based on these effects, the NOAEL for systemic effects was established at 100 mg/kg bw/day. No other details are available (US EPA, 2010).

In a seven-week dermal study F344/N rats and B6C3F1 mice received dermal applications of undiluted dimethoxane for 48 consecutive days. The mean dose was 3000 mg/kg bw/day for rats and 5100 mg/kg bw/day for mice. Reduced body weights were observed in rats and male mice. Increased relative organ weights were reported (e.g. liver, kidney and heart). Skin irritant effects were observed (refer **Skin irritation** section) (NTP, 1989).

In a 13-week toxicity study, dogs were administered the chemical subcutaneously at doses up to 1 mg/kg bw/day. No effects were noted (SCC, 1987).

In another 90-day study, rats were treated subcutaneously with 3, 10 or 30 mg/kg bw/day. No effects were noted (SCC, 1987).

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available data, the chemical is not considered to be genotoxic. The chemical may be metabolised to acetic acid, acetaldehyde and 3-hydroxybutaraldehyde—which is in equilibrium with 2-butenal. Acetaldehyde and 2-butenal were positive in various in vitro and in vivo genotoxic assays and are currently classified as Category 3 mutagenic substances in the HSIS (NICNASa, NICNASb).

In vitro

The chemical (approximately 80 % purity) was assessed in a bacterial reverse mutation assay in *Salmonella typhimurium* (TA1535, TA1537, TA97, TA98, and TA100) in the presence and absence of rat and hamster S9 mix at doses of 0.033, 0.100, 0.333, 1.000, 2.000, 2.150, 3.333, 4.444, 5.500, 5.555, and 6.666 mg/plate. The chemical was mutagenic in strain TA100 with metabolic activation. It was not mutagenic in strain TA100 without metabolic activation or in strains TA98, TA1535, or TA1537 with or without metabolic activation. The lowest positive dose tested was 3.333 mg/plate in strain TA100 without activation (NTP, 1989). In another Ames assay, the chemical was not found to be mutagenic in five strains with or without metabolic activation (US EPA, 1996). No other details of this study are available.

The chemical (approximately 80 % purity) induced sister chromatid exchanges (SCEs) and chromosomal aberrations (CA) in Chinese hamster ovary (CHO) cells both with or without S9 metabolic activation. Significant increases in SCEs, within a dose range of 1.1 –12.6 µg/mL in the absence of S9 and over a range of 11–110 µg/mL with S9 metabolic activation were observed (NTP, 1989). In a CA assay, without S9, doses of 20.2 and 22.7 µg/mL produced abnormal metaphases in 100 % of cells; with S9, 75 % of cells exposed to > 176 µg/mL showed aberrations. In a different study, the chemical was clastogenic in CHO cells with activation but was negative without activation (US EPA, 1996). No details of this study are available

The chemical was negative in the a hepatocyte unscheduled DNA synthesis assay (US EPA, 1996). Primary rat hepatocyte cultures were exposed to the chemical (93 % purity) at concentrations ranging from 0.506 to 5060 µg/mL for 20.7 hours (California EPA, 2004).

In vivo

In a mouse micronucleus test there was no increase in micronuclei in the bone marrow polychromatic erythrocytes. Male mice (CD-1) received the chemical (93 % purity) at doses of 0, 500, 1000 and 2000 mg/kg bw by oral gavage on two consecutive days (California EPA 2004; US EPA, 2010).

The chemical was negative in an in vivo unscheduled DNA synthesis in rat primary hepatocyte cultures. Male F344 rats were given a single oral dose of test article by gavage at 0 (corn oil), 1000 or 2000 mg/kg. Animals were sacrificed at 2–4 hours and 14 –16 hours after dosing. Signs at 1000 and 2000 mg/kg bw seen prior to the 14–16 hour sacrifice included hypoactivity, red crust around the nose, mouth and/or eyes and laboured breathing. Hepatocytes were isolated, incubated with tritiated thymidine for 4 hours followed by an additional incubation of 16 to 20 hours before processing. There was no evidence of unscheduled DNA repair (California EPA 2004; US EPA, 2010).

The chemical (approximately 80 % purity) induced sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered by abdominal injection to Canton-S wild-type adult males that resulted in approximately 30 % mortality. Following treatment, males were mated individually to three harems of Basc virgin females to produce three broods for analysis. A dose of 10,000 ppm when administered to males by injection was positive in this assay. No induction of reciprocal translocations was observed in adult males after treatment (NTP, 1989).

QSAR

The QSAR modelling for genotoxicity using the OECD QSAR Toolbox (v.3.4) indicated that there were DNA and protein binding alerts for the chemical. However, the chemical gave a negative prediction for genotoxicity (in vitro and in vivo assays) based on OASIS-TIMES (v.2.27.19). Predictions were within the applicability domain of the model.

Carcinogenicity

Considering the animal studies conducted, there is equivocal evidence of carcinogenicity through the oral route. The toxic effects of dimethoxane appeared to be associated with the primary site of chemical application. The available data do not warrant hazard classification.

In carcinogenicity studies, F344/N rats and B6C3F1 mice were administered the chemical (80 % purity with none of the impurities exceeding 3 %) in corn oil by gavage for 5 days per week for 15 months or 2 years (NTP, 1989).

In the 2-year studies, no significant differences in survival were observed between any groups of rats or mice at any dose. There was no evidence of carcinogenic activity of the chemical in male F344/N rats receiving 62.5 or 125 mg/kg bw/day (highest dose tested) or female F344/N rats receiving 125 or 250 mg/kg bw/day (highest dose tested). There was equivocal evidence of carcinogenic activity of the chemical in male B6C3F1 mice, as indicated by an increased incidence of forestomach neoplasms. There was no evidence of carcinogenic activity for female B6C3F1 mice receiving 250 or 500 mg/kg per day. Acanthosis and hyperkeratosis occurred at increased incidences in the forestomach of high dose rats. Inflammation, acanthosis with hyperkeratosis, and focal hyperplasia occurred at increased incidences in the forestomach of dosed mice. The incidence of squamous cell papillomas of the forestomach was increased in high dose male mice (vehicle control, 2/47; low dose, 3/47; high dose, 7/50). A squamous cell carcinoma of the forestomach was present in another high dose male mouse. This increase in squamous cell papillomas was not significantly different from controls but the incidence exceeded the highest observed in historical corn oil gavage vehicle controls (3/49). The aetiology of the forestomach lesion is unknown. Whether the marginal increase observed in mice is related to direct carcinogenesis or to chronic irritation of the forestomach mucosa is uncertain. No incidence of hyperplastic or neoplastic lesions outside of the stomach other than a single squamous cell papilloma in the oesophagus of a low dose male mouse were seen. There was no cellular atypia or dysplasia to suggest progression to malignancy (NTP, 1989).

Harderian gland adenomas were seen in two mice killed at 15 months: one high dose male, one high dose female. A Harderian glad adenocarcinoma was seen in one second-high dose female mouse. However, no increase in the incidence of Harderian gland neoplasms was seen in the 2-year studies (NTP, 1989).

The findings of no evidence of carcinogenicity in the 2-year study in rats appear to contrast with the carcinogenic response observed in a drinking water study in male Wistar rats. In this study, Wistar rats were given a 1% solution of dimethoxane in the drinking water daily for 613 days, to give an average total dose of 237 g/animal (equivalent to 850 mg/kg bw per day). Malignant tumours developed in 14/25 rats that received the chemical, including hepatomas (8), lymphosarcomas (1), transitional-cell carcinoma of the kidney (1), leukaemia (1), epidermoid carcinoma of the neck (1) and subcutaneous fibrosarcoma (1). One lymphosarcoma was seen in the control group. The disparity seen between the two carcinogenicity studies could be related to the differences in dosing. In the drinking water studies, animals were exposed continuously to the chemical and its hydrolysis products, whereas in the gavage studies, a single bolus dose was used. Also, the dose in the drinking water study (equivalent to 850 mg/kg) was three to seven times the highest doses (125 and 250 mg/kg) received by male or female rats in the gavage study (IARC, 1977).

The metabolite, 2-butenal, was shown to induce hepatocellular carcinomas in F344 male rats that received 7.3 mg/kg bw/day dimethoxane in a drinking water study. However, the study was only carried out in males and using 2 doses. The tumour incidences were also not dose related. Classification was not warranted (NICNASb). The metabolite, acetaldehyde, is classified as hazardous as with the risk phrase 'Limited evidence of carcinogenic effect' (Carc. Cat. 3; R40) in HSIS (Safe Work Australia) based on tumours of the respiratory tract in rats and hamsters following inhalation exposure, particularly adenocarcinomas and squamous cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters (NICNASa).

The International Agency for Research on Cancer (IARC) has classified dimethoxane as 'Not classifiable as to its carcinogenicity to humans' (Group 3) based on inadequate evidence for carcinogenicity in humans and animals (IARC, 1987). This does not take into account the NTP studies conducted later. However, the relevance of rodent forestomach tumours to humans is questionable and therefore the NTP studies do not strengthen the evidence for carcinogenicity.

Reproductive and Developmental Toxicity

The chemical is not considered to be a reproductive or developmental toxicant.

No evidence of developmental toxicity was observed in a gavage developmental study in SD rats given doses of dimethoxane at 0, 60, 300, or 900 mg/kg bw/day (92 % purity). Several skeletal variations were observed in the mid- and high-dose pups in this study and the incidence was slightly increased over the controls. This included incomplete ossification of several bones; however, these increases were not statistically significant. The NOEL for maternal toxicity was established at 300 mg/kg bw/day. The maternal LOAEL was determined to be 900 mg/kg bw/day, based on reduced body weight gain and food consumption, and excessive salivation. The developmental NOAEL was considered to be 900 mg/kg bw/day (US EPA, 2010).

No adverse effects on the histopathology of reproductive organs of rats or mice were reported following the administration of the chemical in the 2-years carcinogenicity study (NTP, 1989).

No reproductive effects were seen with the two metabolites acetaldehyde and 2-butenal (NICNASa, NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation. The chemical may also be irritating to the respiratory tract.

Hydrolysis products of the chemical have evidence of carcinogenicity.

Public Risk Characterisation

Given that the main uses identified for this chemical are commercial and non-industrial uses, it is unlikely that the public will be exposed at levels that warrant concern. Although some potential for consumer uses were identified, the incidence of use is expected to be minimal based on overseas data. In addition, the chemical is used in products at low concentrations (refer **Import, manufacture and use** section). Overall, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical health effect, the risk to workers from the chemical is considered high unless adequate control measures to minimise occupational exposure to these chemicals 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.

The data available support an amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

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

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling 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)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

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

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

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal 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:

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

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

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