2-Propenoic acid, (1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] ester: Human health tier II assessment

25 November 2016

CAS Number: 42978-66-5

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.

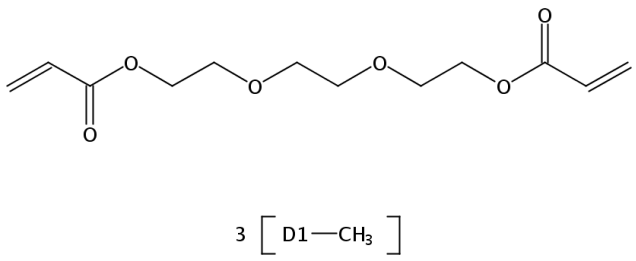
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tripropylene glycol diacrylate (1-methyl-1,2-ethanediyl)bis(oxy(methyl-2,1-ethanediyl)) diacrylate 2-propenoic acid,(1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] ester 2-propenoic acid, 1,1'-(1,3-propanediylbis(oxy-3,1-propanediyl)) ester TGPDA
Structural Formula	
Molecular Formula	C15H24O6
Molecular Weight (g/mol)	300.35
Appearance and Odour (where available)	clear, colourless liquid
SMILES	C(=O)(C=C)OC(C)COC(C)COC(C)COC(=O)C=C

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List with a total reported volume in the range 1000–9999 tonnes per annum (HVICL, 2006).

The chemical has reported site-limited uses, including in the manufacture and production of paper and paper pulp (HVICL, 2006).

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;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) chemical program;
- the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR);
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and
- international publications (Nylander-French & French, 1998; Danish EPA, 2000).

The chemical has reported cosmetic uses, including as a plasticiser and in artificial nails.

The chemical has reported domestic uses, including in:

- adhesives and binding agents;
- surface treatment products; and
- paints, lacquers and varnishes.

Surface coating materials in Sweden typically contain the chemical at 10-30 %, but higher concentrations have been reported (Danish EPA, 2000).

The chemical has reported commercial uses, including:

- in printing and publishing agents;
- as photochemicals in ultra violet (UV) cured inks; and
- in reprographic agents.

The chemical has reported site-limited uses, including in the manufacture, production and processing of paper and paper pulp.

The chemical is listed on the OECD HPV list, the International Council of Chemical Associations (ICCA) HPV working list and the US Environmental Protection Agency High Production Volume list (US EPA HPV).

It should be noted that while international cosmetic and domestic use has been identified through some sources, the Compilation of Ingredients used in Cosmetics in the United States does not report any occurrences of the chemical (CIUCUS, 2011). Furthermore, the chemical is not listed on the US Department of Health & Human Services, Household Products Database or on the Consumer Product Information Database (CPID).

Restrictions

Australian

No restrictions have been identified (SUSMP, 2016).

International

No known restrictions have been identified.

The Swedish Chemicals Agency is developing a risk management option analysis (ECHA).

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; R36/37/38 (irritation)
- R43 (sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical 2-propenoic acid, (1-methyl-1,2-ethanediyl)bis[oxy(methyl-2,1-ethanediyl)] ester, also known as tripropylene glycol diacrylate (TPGDA), is an ester of acrylic acid. Limited data for systemic effects were available for the chemical (particularly repeated dose toxicity data). Where appropriate, data has been included for another diacrylate; hexamethylene diacrylate (CAS No. 13048-33-4). Whilst there are differences in the alcohol metabolites between these chemicals, acrylates most likely react at the site of contact. The potential alcohol metabolites polypropylene glycol (CAS No. 25322-69-4) and tripropylene glycol (CAS No. 24800-44-0) are not considered to pose an unreasonable risk to the health of workers and public health (NICNASa; OECD, 1994).

Toxicokinetics

No data are available for the chemical.

Acrylates are rapidly metabolised. This occurs via two pathways: one mediated by carboxylesterases to hydrolyse the ester linkage to form acrylic acid and the relevant alcohol; and the second is through conjugation with glutathione, either by a spontaneous Michaelis addition reaction, or by glutathione-S-transferase catalysis. The second pathway is the major route of detoxification of acrylates. Conjugation of acrylates by glutathione is expected to be proportional to the number of functional acrylate groups (Danish EPA, 2000; NICNASb).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bodyweight (bw).

The chemical was assessed for acute oral toxicity in a study conducted according to OECD test guideline (TG) 423 (acute oral toxicity—acute toxic class method). Six female Wistar rats were dosed with the chemical via oral gavage at 2000 mg/kg bw. Animals were observed for 14 days after administration. No mortalities occurred during the study, no treatment-related changes in body weights were reported and no macroscopic pathological abnormalities were noted in any of the animals examined at necropsy. On the basis of this study, an LD50 of >2000 mg/kg bw was determined for acute oral toxicity (REACH).

In a study conducted similarly to OECD TG 401 (acute oral toxicity), the chemical was assessed for acute oral toxicity. Male and female Sprague Dawley (SD) rats (five animals/sex) were dosed with the chemical via oral gavage at 5000 mg/kg bw and observed for 14 days. One female and one male died on days one and two of the study, respectively. Dyspnoea, apathy, staggered gait, scrubby fur and hypersalivation were observed in some animals; however, few details were provided. On the basis of the reported effects, investigators concluded that the oral LD50 is >5000 mg/kg bw (REACH).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats is 3650 mg/kg bw. The LD50 in rabbits is >2000 mg/kg bw.

The chemical was assessed for acute toxicity following dermal exposure in a study conducted similarly to OECD TG 402 (acute dermal toxicity). Albino rabbits of unspecified sex (four animals/dose) were administered the chemical at 0.315, 0.795, 1.99 and 5.0 mL/kg bw. The chemical was applied to the shaved skin of animals, and left for 24 hours under occlusive patches. No animals died in the 0.315 and 0.795 mL/kg bw groups. One animal died in the 1.99 mL/kg bw group and two animals died in the highest dose group. The test material produced slight to moderate erythema and oedema. On the basis of these findings, investigators reported a dermal LD50 of 3650 mg/kg bw (REACH).

The chemical was assessed for dermal acute toxicity in a study conducted similarly to OECD TG 402 (acute dermal toxicity). The shaved and abraded skin of 10 New Zealand White (NZW) rabbits (five animals/sex) was exposed to the test chemical at 2000 mg/kg bw under occlusive conditions for 24 hours. All 10 animals survived until the end of the 14-day observation period. Clinical signs were observed during the study, including faecal staining, decreased activity and decreased food consumption in two animals. Six animals showed pathological findings including spleen, liver and kidney discolouration. At 24 hours, males exhibited well-defined to severe erythema accompanied by very slight or moderate oedema. At the same time-point, females exhibited slight or well-defined erythema accompanied by severe oedema. On the basis of these results, investigators determined that the dermal LD50 was >2000 mg/kg bw under these conditions (REACH).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure. No mortality was observed following exposure to saturated vapours of the chemical.

A study was conducted to assess the potential for the chemical to cause acute inhalation toxicity in SD rats. Six animals of each sex were exposed to a saturated vapour of the chemical via nose-only inhalation for a period of seven hours. The concentration to which animals were exposed is uncertain. Animals were observed for a period of 14 days after exposure. No animals died during the study. Some animals showed snout-cleaning behaviour following dosing. No gross pathological findings were reported (REACH).

In another acute inhalational toxicity study, three SD rats of both sexes were exposed to a saturated vapour of the chemical (0.41 mg/L) for a period of seven hours in whole-body inhalation chambers. Animals were observed for a period of 14 days after exposure. No animals died during the study. Some animals exhibited snout-cleaning and accelerated, intermittent breathing. On the basis of these findings, investigators reported a median lethal concentration (LC50) of >0.41 mg/L (REACH).

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). Whilst no data are available to evaluate this classification, irritation effects have been observed in dermal and ocular irritation studies.

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). Slight to moderate irritation was observed in a number of studies in rabbits. Overall, the available data support this classification.

A dermal irritation study was conducted with the chemical according to OECD TG 404 (acute dermal irritation/corrosion). The skin of three NZW rabbits (sex not specified) was exposed to 0.5 mL of undiluted chemical under semi-occlusive conditions for a period of four hours. Average oedema scores of 2 and average erythema scores of 2.67 were reported. Investigators reported that the single semi-occlusive application of the chemical to intact rabbit skin elicited persistent, well-defined to moderate dermal irritation (REACH).

The chemical produced slight irritant effects in two studies conducted similarly to OECD TG 404. In each study, three NZW rabbits were exposed to the chemical under semi-occlusive conditions for four hours. The chemical produced slight oedema and erythema which was reversible in all animals (REACH).

In another study, the chemical was assessed for skin irritation in Vienna rabbits. The skin (abraded or intact) of animals (six animals per group) was exposed to the chemical (0.5 mL) for 24 hours under occlusive dressings. Animals were observed for a period of eight days after removal of the test material. The results of the study are as follows: for intact skin, mean erythema score was 2.6 (not fully reversible), mean oedema score was 2.75 (not fully reversible). For abraded skin, mean erythema (not fully reversible) score was 2.55, mean oedema score was 3 (not fully reversible). Other signs of local effects included scaling of skin and necrosis (REACH).

In another study, the shaved skin of six NZW rabbits (sex not specified) was exposed to 0.5 mL of the undiluted chemical under occlusive conditions, for a period of 24 hours. Animals were observed for a period of 14 days following application. The mean scores for erythema and oedema were 2.5 and 1.8, respectively. Based on these effects, the investigators determined that the chemical is a dermal irritant (REACH).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). Slight to moderate irritation was observed in studies in rabbits. Overall, the available data support this classification.

The chemical was assessed in an ocular irritation study similar OECD TG 405. The eyes of Vienna white rabbits (three males and three females) were exposed to the test chemical (0.1 mL, single exposure). Animals were observed for eight days. Ocular effects included ulceration, loss of hair at the border of the eye lids, scars on the eyelids and narrowing of the pupil. The mean

scores for corneal opacity, iridial irritation, conjunctival reddening and oedema formation were 1.17, 1, 1.94 and 1.39, respectively. Effects were not fully reversible within the observation period. On the basis of these results, the test chemical was considered to be an ocular irritant (REACH).

The chemical was assessed for ocular irritation in a study with three New Zealand White rabbits, conducted according to OECD TG 405 (acute eye irritation/corrosion). One eye of each animal was treated with 0.1 mL of undiluted test material and left unwashed for 24 hours. Animals exhibited signs of ocular irritation within 72 hours, including suppuration, pupil contraction, haemorrhage and scleral vessel prominence in a circumscribed area. The average scores for corneal opacity, iridial irritation, conjunctival redness and chemosis were calculated to be 1.0, 0.44, 2.33 and 1.67, respectively. Ocular effects were fully reversible within seven days (REACH).

Sensitisation

Skin Sensitisation

Polyfunctional acrylates are considered more potent contact sensitisers than simple monofunctional acrylates (Nylander-French, 1998; Danish EPA, 2000). The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia). Whilst consistent results were not observed, positive results reported in some animal studies and observations of contact dermatitis in humans support this classification.

The chemical was assessed for skin sensitisation in an OECD TG 429 (skin sensitisation: local lymph node assay (LLNA)) study in female CBA mice (six/animals/dose). Animals were administered the test chemical at 0, 1, 3 and 10 % (in acetone), once daily, for three consecutive days. The test substance (25 µl per application site) was applied epicutaneously to the dorsal part of both ears of each animal. Draining auricular lymph nodes were excised and assessed for cellular proliferation. No signs of systemic toxicity were observed. The test substance induced a statistically significant increase in cell proliferation in the auricular lymph nodes, at all doses tested. Ear weights were statistically significantly increased in the 3 and 10 % dose groups, consistent with observed signs of irritation. No stimulation indices were reported; however, on the basis of these effects, investigators concluded that TPGDA was a skin sensitiser under these experimental conditions (REACH).

A mouse LLNA was conducted according to OECD TG 429 (skin sensitisation) to assess the skin sensitisation potential of TPGDA. The ears of male CBA mice (four animals/dose) were topically administered the test chemical at 3, 10 and 30 % (in acetone). The chemical induced a greater-than three-fold lymph node cell proliferation in all groups. Given the irritant effects observed, the non-dose-dependent cell proliferations could not definitively be attributed to the sensitising effect of the test chemical. On the basis of these effects, the investigators considered the chemical likely to be a skin sensitiser (REACH).

A guinea pig maximisation test (GPMT) was conducted similarly to OECD TG 406 to assess the potential for TPGDA to act as a skin sensitiser. Hartley guinea pigs were inducted via intradermal injection at 1, 2.5, 5 and 8.5 % (six animals) and were challenged at the same concentrations via epicutaneous application (in ethanol:saline 1:4 or acetone:olive oil 4:1). The 1, 2.5 and 5 % groups consisted of 10 animals each, and the 8.5 % group consisted of six animals. Few experimental details were reported. Following assessment of animals 48 hours after challenge, investigators calculated the intradermal concentration required to sensitise half the guinea pigs to be 3.5 %. On the basis of this finding, the chemical was considered to be a skin sensitiser (REACH).

In another GPMT, the chemical (purity unknown) produced positive reactions in 11 out of 15 animals tested. Concentrations administered for intradermal inductions, topical induction and challenge were 1 % in olive oil:acetone, 25 % in petrolatum and 25 % in petrolatum, respectively. The same study showed cross-reactions with several other multifunctional acrylates (Danish EPA, 2000). An identical study with acetone as a vehicle was negative. This is considered to be due to the occurrence of a polymerisation process in acetone (Danish EPA, 2000).

Two GPMT studies, in which the chemical was stabilised with hydroquinone methyl ether, were negative (Danish EPA, 2000).

In a non-guideline study, six Hartley guinea pigs of both sexes were induced and challenged with the test chemical at 0.4 and 4.1 %, respectively. Inductions were conducted by intradermal injection and challenge exposures were conducted epicutaneously. Very few experimental details were provided. The first positive skin reaction was at day 28. The number of sensitised animals was not reported. Study authors indicated that the test chemical produced effects consistent with weak sensitisation (Danish EPA, 2000; REACH).

Observation in humans

There have been a number of reported cases of occupational contact dermatitis following exposure to the chemical, including in silk screen workers, a dental nurse and workers in furniture companies (Danish EPA, 2000).

Positive patch test reactions have been observed with the chemical in petrolatum at concentrations down to 0.01 % (Kanerva, 2000).

Repeated Dose Toxicity

Oral

No data are available for the chemical. Based on data for a related diacrylate, repeated oral exposure to the chemical is not expected to cause serious damage to health.

Another diacrylate, hexamethylene diacrylate, was assessed for oral repeat dose toxicity in an OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) study. Crl:CD(SD) rats of both sexes (24 animals/dose) were administered the chemical in feed at 75, 250 or 750 mg/kg body weight (bw)/day, via oral gavage. Males were dosed for 14 days prior to mating and were dosed throughout the mating period for a total of 28 doses. Females were dosed for 14 days prior to pairing and were dosed until lactation day four, for a total of 41-49 doses; females that failed to deliver were dosed through to euthanasia (post-mating or post cohabitation day 25) for a total of 39-52 doses. Males were paired for mating with females at the same dose level. An extensive range of indicators of maternal and paternal toxicity were assessed (including clinical, physiological, biochemical and histological parameters). Reproductive toxicity parameters were also assessed.

Changes in clinical chemistry were observed, including increases in mean concentrations of: urea nitrogen, bile acids, alanine aminotransferase (ALT), cholesterol and triglycerides. Altered mean calcium and phosphorous concentrations were generally observed only at the high dose. Increased ALT concentrations were also observed in the mid dose females. Increased liver weights were observed in high dose males and females. Histopathological changes were noted in the stomach and liver including:

- mild to moderate epithelial hyperplasia, and mild to severe hyperkeratosis in the non-glandular portion of the stomach in mid and high dose animals (dose-dependent); and
- vacuolation of periportal hepatocytes at all doses (dose dependent).

The No Observed Adverse Effect Level (NOAEL) for parental toxicity was determined to be 75 mg/kg bw/day.

Dermal

Based on the available data, repeated dermal exposure to the chemical is not expected to cause serious damage to health, with the exception of local irritant effects.

In a 90-day dermal repeated dose toxicity study in rats, an NOAEL of 67 mg/kg bw/day was reported. Effects observed at higher concentrations (200 mg/kg bw/day) included significantly reduced bodyweight in males and some changes in neurobehaviour (decreased corneal reflex and moderately decreased toe pinch response). Irritation was observed at all doses (Danish EPA, 2000; REACH).

Inhalation

No data are available.

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

The chemical was assessed in a bacterial reverse mutation assay (Ames test) conducted according to OECD TG 471 (bacterial reverse mutation assay). *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 were incubated with the chemical at concentrations up to 5000 µg/plate, in the presence or absence of metabolic activation. The chemical failed to cause an increase in the number of revertant bacterial colonies at any concentration tested, in any strain, either in the presence or absence of metabolic activation (REACH).

The chemical was assessed in a bacterial reverse mutation assay conducted according to OECD TG 471. *S. typhimurium* strains TA 1537, TA98, TA100, TA 1535 and *Escherichia coli* WP2 uvr A strain were incubated with TGPDA at concentrations up to 5000 µg/plate, in the presence or absence of metabolic activation. An ambiguous, non-dose dependent increase in the number of mutant colonies was observed for *S. typhimurium* strain TA1535 in the presence of metabolic activation (REACH).

The chemical was assessed in an Ames test according to OECD TG 471. *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 were incubated with the test material at concentrations up to 5000 µg/plate, in the presence or absence of metabolic activation. The test substance was found to be non-mutagenic under these experimental conditions (REACH).

In another Ames test conducted according to OECD TG 471. *S. typhimurium* strains TA 1535, TA 1537, TA1538, TA 98 and TA 100 were incubated with the test material up to 50.0 µl per plate, in the presence or absence of metabolic activation. The test substance was found to be non-mutagenic under these test conditions (REACH).

The chemical was positive in an in vitro mammalian cell gene mutation test in mouse lymphoma L5178Y cells. Positive responses were observed in experiments with different concentration ranges, both in the presence and absence of metabolic activation (Danish EPA, 2000; REACH).

The chemical was assessed for genotoxicity in an in vitro study conducted according to OECD TG 476. Chinese hamster ovary epithelial cells were incubated with TPGDA at concentrations up to 30 µg/mL in the absence of metabolic activation and up to 140 µg/mL in the presence of metabolic activation. The test chemical did not induce any statistically significant evidence of genotoxicity at any concentration tested, either with or without metabolic activation (REACH).

In vivo

The chemical was assessed for its genotoxic potential in an in vivo study conducted according to OECD TG 474 (mammalian erythrocyte micronucleus test). Male NMRI mice (five animals/dose) were administered the chemical at 87.5, 175 or 350 mg/kg bw via a single intraperitoneal injection. Femoral bone marrow was harvested from animals 24 hours after exposure for the low and mid-dose groups, and 48 hours after exposure for the high dose group. No less than 2000 polychromatic erythrocytes from each of the animals of every test group were evaluated and investigated for micronuclei formation. There was no statistically significant increase in the number of micronuclei observed in the marrow of animals at any dose tested, indicating a lack of clastogenicity. A dose-dependent inhibition of erythropoiesis, determined from the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE), was detected from the 87.5 mg/kg bw dose and higher (REACH).

The chemical was assessed in a mammalian micronucleus test according to OECD TG 474. Male CD-1 mice (five animals/dose) were administered the test chemical via oral gavage at 500, 1000 or 2000 mg/kg bw. This followed a range finding study conducted in both sexes. Bone marrow was harvested from animals and the rate of micronuclei formation in erythrocytes was assessed. The chemical did not cause a statistically significant increase in micronuclei formation at any dose tested. The chemical was not cytotoxic to the bone marrow (REACH).

The chemical, and a lacquer containing the chemical, was applied dermally to Tg.AC mice (three times/week for 20 weeks). Peripheral blood leukocytes were evaluated for DNA damage (single-strand breaks, alkali labile sites, DNA crosslinking) at weeks four, eight, 12, 16, and 20 by using the alkaline (pH >13) single cell gel assay. The extent of DNA migration and the frequency of micronucleated PCE and NCE in blood were not altered. The percentage of PCE was increased (indicating increased rate of erythropoiesis) in mice treated with the chemical (Danish EPA, 2000; REACH).

Carcinogenicity

The carcinogenicity of the chemical was investigated in a non-guideline study in 50 male C3H mice. Animals were dermally exposed to the test chemical (25 mg), twice weekly for 80 weeks. Few experimental details were provided, however, under the test conditions no skin tumours were observed in animals treated with the chemical (REACH). The study has been reported as inadequate for the evaluation of carcinogenic potential (Mortensen, 1991; REACH).

An increased number of skin tumours were observed in TPGDA-treated female Tg.AC (v-Ha-ras) mice in a twenty week, short-term tumourigenesis study. The chemical was applied topically three times a week for 20 weeks at doses of 1, 5 or 10 µmoles/mouse, either in the form of technical quality TPGDA or as a lacquer intended for UV-cured coatings. The chemical TPGDA and reference Lacquer A (equimolar for TPGDA) at 5 or 10 µmoles/mouse induced a marginal dose-related increase in papillomas between six and 12 weeks of treatment. A maximum number of papillomas per mouse was reached between 19 and 20 weeks of treatment. The data suggest that a threshold exists, which can be readily saturated. Ethyl acrylate was negative in this study. These results indicate that the chemical is significantly more potent than ethyl acrylate for inducing the skin reporter phenotype and may be predicted to be carcinogenic in long-term cancer bioassays at the site of contact (Nylander-French, 1998; Danish EPA, 2000).

Differences in mouse strain, vehicle and dose rate may have contributed to the difference of induction of skin papillomas in the two studies (Nylander-French, 1998).

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

The chemical was tested in a non-guideline study for developmental toxicity. The chemical was administered to 20 pregnant female rats via oral gavage at 250 mg/kg bw/day, through gestation days (GD) 6-15. No embryotoxic or teratogenic effects were observed (Danish EPA, 2000; REACH).

Another diacrylate, hexamethylene diacrylate was assessed for developmental toxicity in a study conducted similarly to OECD TG 414 (prenatal developmental toxicity study). The chemical was administered to 22 mated female SD rats via oral gavage at 750 mg/kg bw/day, through GD 6-15. Embryotoxic effects were observed (delayed ossification in various bone structures); however, the authors indicated that these effects were secondary to maternal toxicity. Therefore, an NOAEL of 750 mg/kg bw/day was determined for developmental toxicity for the test chemical under these conditions (REACH).

Hexamethylene diacrylate was assessed for reproductive toxicity in an OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) study. Crl:CD(SD) rats of both sexes (24 animals/dose) were administered the chemical in their feed at 75, 250 or 750 mg/kg bw/day, via oral gavage (refer to **Repeated dose oral toxicity** for more information). There were no statistically significant treatment-related effects in any of the reproductive toxicity parameters assessed in this study (offspring viability, clinical signs, body weights, gross pathology). Therefore, an NOAEL of 750 mg/kg bw/day was determined for reproductive toxicity (REACH).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation. The chemical may also promote the induction of skin tumours. A non-genotoxic mechanism is considered likely. The chemical can also cause skin and eye irritation.

Further assessment may be required if more information becomes available on the carcinogenic potential of this chemical.

Public Risk Characterisation

Although use in cosmetic and domestic products in Australia is not known, widespread consumer use is not expected as American data sources do not indicate current use of the chemicals (see **Import, Manufacture and Use** section).

However, the associated risks of contact dermatitis, as well as uncertainty in carcinogenic potential, give cause for concern and therefore, it is recommended that further assessment or changes in risk management may be required should information become available to indicate significant consumer exposure to the chemical in Australia.

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 chemical 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 local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking 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. Whilst the carcinogenicity of the chemical cannot be fully evaluated, controls put in place due to the sensitisation properties of the chemical are considered warranted, to minimise any potential risk.

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.

Further assessment may be required if information becomes available on the carcinogenic potential of this chemical or information becomes available to indicate significant consumer exposure to the chemical in Australia.

Regulatory Control

Public Health

If any information becomes available to indicate significant consumer exposure to the chemical in Australia, risks to public health and safety may have to be managed by changes to the Poisons Standard.

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 eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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 consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal, 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 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 chemicals, 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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