Ethanol: Human health tier II assessment

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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	Ethyl alcohol Alcohol Anhydrol Ethyl hydrate Methyl carbinol
Structural Formula	
Molecular Formula	C2H6O
Molecular Weight (g/mol)	46.07
Appearance and Odour (where available)	Clear, colourless liquid with a characteristic pleasant odour and burning taste.
SMILES	C(C)O

Import, Manufacture and Use

Australian

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

The chemical has reported cosmetic use.

The chemical has reported domestic use as a cleaning/washing agent.

The chemical has reported commercial use including:

- as petrol additives/substitutes such as ethanol blended fuels; and
- as a solvent

The chemical has reported site-limited use for the manufacture of other chemicals.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 10000–99999 tonnes.

The National Pollutant Inventory (NPI) holds data for all sources of emissions of the chemical in Australia.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use including:

- as a solvent and as an astringent;
- as a fragrance ingredient;
- in antifoaming, antimicrobial, and viscosity decreasing agents; and
- in masking.

The US Household Products Database states a concentration of up to 65 % (aerosol) and 100 % (liquid) for personal care use.

The chemical has reported domestic use including in:

- adhesives (binding agents) and fillers;
- anti-condensation agents;
- aerosol propellants;
- colouring agents;
- cleaning/washing agents;
- flame retardants and extinguishing agents;

- dyes and printing inks;
- insulating materials & corrosion inhibitors;
- polishes and surface coatings including paints, lacquers and varnishes;
- odour agents;
- surface treatment; and
- surface-active agents.

The US Household Products Database states a concentration of up to: 5 % (aerosol) and 31 % (liquid) for use in arts and crafts; 5 % (aerosol) and 99 % (liquid) for use in auto products; 70 % (aerosol) and 85 % (liquid) for use in home maintenance; 90 % (aerosol) and 78 % (liquid) for use inside the home; and 100 % (aerosol) for use in landscape/yard/mainteance.

The chemical has reported commercial use including:

- as a solvent in various formulations/products;
- in absorbents and adsorbents;
- in anti-freezing, anti-set-off, and adhesive agents;
- in grinding materials;
- in conductive agents;
- in construction materials and in cutting fluids;
- in dust binding agents;
- in hydraulic fluids and additives;
- in fuels and fuel additives;
- in explosives;
- in lubricants and additives;
- in impregnation materials;
- in process regulators, softeners and fixing agents;
- in reprographic agents;
- in photo chemicals and pH-regulation agents;
- in tanning agents;
- in welding and soldering agents;
- as a viscosity adjustor and anti-static agent;
- as a flux agent for casting or joining materials; and
- as a solvent.

The chemical has reported site-limited use including:

- in heat transfer agents;

- in laboratory chemicals;
- in electroplating agents; and
- as an intermediate for the production of synthetic chemicals.

The following non-industrial uses have been identified internationally including:

- in pharmaceutical preparations (rubbing compounds, lotions, tonics, colognes, mouthwash products);
- in human and veterinary medicines;
- in pesticides;
- in food/feedstuff flavourings and nutrients;
- in alcoholic drinks (beer, wine, spirits); and
- as a topical agent to prevent skin infections.

Restrictions

Australian

Denatured ethanol (methylated spirits) is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP, 2013) in Schedule 5 with the following entry:

'METHYLATED SPIRIT(S) (being ethanol denatured with denatonium benzoate, methyl isobutyl ketone and fluorescein) **except**:

(a) when included in preparations or admixtures; or

(b) when packed in containers having a capacity of more than 5 litres'.

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label (SUSMP, 2013).

Ethanol is also listed in the Poisons Standard (SUSMP, 2013) in Appendix B (Part 3).

Appendix B (Part 3) are the substances that are considered not to require control by scheduling due to their low toxicity.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not classified for health hazards on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

The chemical has an exposure standard of 1880 mg/m³ (1000 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 960–1920 mg/m³ (500-1000 ppm) in countries such as Canada, Denmark, Germany, Sweden, South Africa, Switzerland, United Kingdom, and the United States of America.

An exposure limit (STEL) of 1900–1920 mg/m³ (1000 ppm) in countries such as Canada, Sweden, and Switzerland.

Health Hazard Information

Toxicokinetics

Although the chemical has been reported to be readily and rapidly absorbed following oral exposure in humans, the chemical is poorly absorbed following dermal exposure. Even though approximately 60 % of inhaled chemical vapour is absorbed, a large proportion of inspired chemical is deposited in airway linings that is then released with expired ethanol-free alveolar air.

Following absorption, the chemical is widely distributed in body water and metabolised mainly in the liver. Other tissues such as the kidney, stomach and intestines also metabolise the chemical, but to a lesser extent. The first metabolic step is oxidation to acetaldehyde by alcohol dehydrogenase followed by rapid conversion to acetate via acetaldehyde dehydrogenase. Acetate is then released into the blood stream to be converted in peripheral tissues to acetic acid and ultimately to CO_2 and water. Even though the chemical is mainly metabolised through alcohol dehydrogenase, other hepatic pathways for oxidation have also been described, including a microsomal system in endoplasmic reticulum and a catalase system in peroxisomes. Although the capacity of the alcohol dehydrogenase enzyme system is saturable at low blood ethanol levels, the rate of metabolism of the chemical in the liver is not dependent on the concentration of the chemical except at very low or very high concentrations. Under conditions of occupational exposure and use of cosmetic and domestic products, the metabolism of the chemical through alcohol dehydrogenase dominates in the liver and does not become saturated. The chemical equilibrates rapidly between blood and milk; milk levels are about 90–95 % of simultaneous blood levels.

Although the predominant route of excretion of the chemical is in the urine, the chemical is also excreted in exhaled air and sweat. Excretion occurs mainly as metabolites with a small amount (5–10 %) excreted unmetabolised. The chemical does not accumulate in the body (OECD, 2005; HSDB; REACH).

Acute Toxicity

Oral

The chemical has low acute toxicity by oral exposure in animal tests. The median lethal dose (LD50) in rats is >2000 mg/kg bw. Observed sub-lethal effects included central nervous system depression, e.g. inebriation, disturbances of gait, dose-related decreases in responses to painful stimuli, respiratory depression, and coma. Deaths were reported due to cardiorespiratory failure (OECD, 2005; HSDB; REACH).

Dermal

Few studies are available on the dermal toxicity of the chemical. A poorly documented rabbit study reported death in one of four animals following a dose of 20000 mg/kg bw. Although limited data are available, the apparent low dermal toxicity from this study is regarded as consistent with low uptake of ethanol through intact skin. The median lethal dose (LD50) in rats is greater than 2000 mg/kg bw. Observed sub-lethal effects were not reported for the study (OECD, 2005; REACH).

Inhalation

The chemical has low acute toxicity by inhalation exposure in animal tests. The lowest reported median lethal concentration (LC50) is 124.7 mg/L/four hours in rats. Observed sub-lethal effects included attempts to escape, reddish-watery eyes, nasal secretions, closing of eyelids, snout wiping, intermittent respiration, loss of pain reflex, abdominal position, and apathy (OECD, 2005; REACH).

Observation in humans

Consumption of beverages containing the chemical has been associated with symptoms of intoxication (drowsiness, loss of concentration). However, there is no evidence of such symptoms occurring following dermal or inhalation exposures (OECD, 2005; HSDB).

Corrosion / Irritation

Skin Irritation

The chemical is not regarded as irritating to skin.

In a skin irritation study conducted in accordance with OECD Test Guideline (TG) 404, the chemical was applied to six New Zealand White rabbits for four hours using exposure chambers. The mean score for erythema was one at 24 hours and remained zero at all other time points (48, 72 hours); the mean score for oedema remained zero at all time points (24, 48, 72 hours). The chemical was concluded not to be irritating to the skin of rabbits. Another skin irritation study in rabbits, where the chemical was applied under occlusion for 24 hours, also showed only very slight skin irritation (OECD, 2005; REACH).

Eye Irritation

The chemical produced irritant effects in several eye irritation studies in rabbits. While the severity of these effects was not consistent across all the studies, these were sufficiently severe in some studies to support classification, particularly under the Globally Harmonised System of Classification and Labelling of Chemicals (refer to **Recommendation** section).

In an eye irritation study conducted in accordance with US Federal guideline (Fed. Reg. Vol. 38, No. 187, 1973), the chemical (0.1 mL) was applied on the conjuctival sac of one eye of each of three New Zealand White rabbits. Irritation responses were observed at 24, 48 and 72 hours and eight days following application. Mean Draize scores following grading at 24, 48 and 72 hours for three rabbits were 1 for corneal opacity, 0.22 for iritis, 2.45 for conjunctivitis, and 1.89 for chemosis. Mean Draize scores following grading at day eight were 0.67 for corneal opacity, 1.67 for conjunctivitis, and 1.33 for chemosis. While iris lesions were fully reversible by day eight, other eye lesions were not fully reversible at this time. Given the observation period did not extend to 21 days, it is difficult to conclude any findings on the reversibility of the irritation. The average response of 2/3 animals was sufficiently severe in terms of conjunctival effects (>2.5) and chemosis (≥2) observed, that classification as an eye irritant is warranted (REACH).

In another eye irritation study (OECD TG 405), the chemical (0.1 mL) was applied to the eyes of three rabbits (strain not specified) and observed up to 14 days. Mean Draize scores at 24, 48 and 72 hours were 2.11 for conjunctivitis, 1.33 for chemosis, 0.44 for iritis, and 1.11 for corneal opacity. Although all symptoms subsided by day 14, conjunctivitis was still present

at day seven. As positive responses for corneal opacity (mean score >1 for 2/3 animals) and conjunctival redness (mean score >2 for 2/3 animals) were noted in the study, the chemical is considered to be an eye irritant (category 2A) (OECD, 2005; REACH).

In an eye irritation study (OECD TG 405), the chemical (0.1 mL) was applied into the lower conjunctival sac of one eye of six New Zealand White rabbits and observed up to 72 hours. Reported average Draize scores at 24, 48 and 72 hours were 2.39 for redness of the conjunctivae, 1.2 for chemosis, 0.28 for iritis, and 1.2 for corneal opacity. As conjuctival redness persisted for 24 hours with a mean score of >2 and corneal opacity was noted with a mean score >1, the chemical is considered to be an eye irritant (category 2A) (OECD, 2005; REACH).

In an eye irritation study conducted in accordance with US Federal guideline (Fed. Reg. 28 (119), 5582, 1963), the chemical (0.1 mL) was applied on the lower lid of one eye of six New Zealand White rabbits. The eyes were examined at 24, 48, and 72 hours and at day seven following administration of the chemical. Mean Draize scores following grading at 24, 48 and 72 hours were 1.72 for conjunctivitis, 1.78 for chemosis, 0.83 for iritis, and 1.28 for corneal opacity. While iris lesions were fully reversible at day seven, other eye lesions were not. Mean Draize scores following grading at day seven were 0.83 for conjunctivitis, 0.83 for chemosis, and 1.17 for corneal opacity. As corneal opacity was noted with a mean score >1, the chemical is considered an eye irritant (category 2A). In addition, whilst mean scores for conjunctival redness and chemosis were <2, scores ≥2 were noted in four out of six animals (OECD, 2005; REACH).

Observation in humans

The chemical is frequently applied to skin as a biocidal surgical wipe (70–80 % concentration) and as a component of cosmetics, personal care, and household cleaning products. There appear to be few documented concerns regarding skin irritation arising from these uses. Direct contact of the eye with the liquid chemical causes immediate discomfort accompanied by reflexive closure of the eye. Even though the acute effect subsides rapidly and the recovery is complete, foreign body type discomfort may persist for a day or two. Although inhaling the chemical at 5000 ppm (9600 mg/m³) has been reported as irritating in humans; lacrimation and coughing are only induced at a much higher concentrations (OECD, 2005).

Concentrations of the chemical attained in humans in the upper gastrointestinal tract after consumption of alcoholic beverages can cause local irritation.

Sensitisation

Skin Sensitisation

The available data indicate that the chemical does not induce skin sensitisation in animals.

The chemical, at 75 % concentration, was used as a solvent in a Magnusson and Kligman guinea pig maximisation test of a polyalkalene glycol. Skin reactions were not observed at challenge with the polyalkalene glycol in 75 % ethanol in either the test or negative control animals (OECD, 2005). In a mouse ear swelling test, no increase in ear thickness was observed following a challenge application of the chemical at 95 % (OECD, 2005; REACH).

In a mouse local lymph node assay (LLNA) (OECD TG429) the chemical, or diethyl phthalate, were used as vehicles to examine the skin sensitisation potential of four test fragrance materials. The concentration of the chemical in this study varied from 0–100 %. The level of induced T-lymphocyte proliferation was low for the chemical compared with that for fragrance materials known to be mild to moderate skin sensitisers, and comparable with the other negative control vehicle (diethyl phthalate). On the basis of a lack of sensitising potential up to a concentration of 100 %, the test concluded that the chemical is an appropriate vehicle for use in a local lymph node assay (REACH).

Observation in humans

Although a literature review of contact reactions to the chemical has noted that the chemical can induce immediate and delayed hypersensitivity reactions in humans following external and internal exposures, the widespread use of the chemical in cosmetics

and in skin antiseptic formulations suggests that skin sensitisation is not of concern (OECD, 2005). A single reported case notes that a patient using a transdermal drug delivery system with ethanol as a solvent experienced erythematous and itchy lesions at patch sites after continuous use. The authors concluded that such adverse effects are only likely under occluded conditions and when used for prolonged periods (REACH).

Repeated Dose Toxicity

Oral

Many repeated dose studies of chemical have been conducted in many species, predominantly with the aim of assessing adverse effects associated with the consumption of alcoholic beverages. Consequently, these are mostly conducted through oral exposure and with doses well in excess of those that might be encountered in occupational exposure or consumer products (OECD, 2005), or unintentional public exposures from environmental contamination.

Considering the lowest observed adverse effect level (LOAEL) available from a 90-day rat study (3600 mg/kg bw/day), and based on the treatment-related effects reported in various repeated dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure, except from exposure to high doses.

In a well-conducted repeated dose toxicity study, the chemical was administered (in a liquid diet) to Sprague Dawley (SD) rats at a 1, 2, 3, 4, 5, and 10 % concentration for 90 days. Water consumption in the 10 % group was reduced relative to controls. There were no adverse clinical signs or mortality during the study. Serum liver enzymes were unaffected by treatment and kidney findings were reported to be minimal. A LOAEL was established at 3 % (approximately 3600 mg/kg bw/day), based on dose-related hepatic yellowing, centrilobular steatosis, increased frequency and severity of Mallory bodies (hyaline), and acidophilic degeneration and necrosis. The no observed adverse effect level (NOAEL) was 2 % (approximately 2400 mg/kg bw/day) (OECD, 2005; REACH).

In another repeated dose toxicity study conducted in accordance with national test guidelines of USA (EPA OPPTS 870.3100), the chemical was administered in drinking water to Fischer 344 (F344) rats and $B6C3F_1$ mice at a single dose of 5 % concentration for 90 days. Even though male rats showed minor changes in thymus weights, and some slight but inconsistent changes in haematology and clinical chemistry, these effects were not considered adverse. Based on water consumption data, this single dose study established a 5 % nominal NOAEL for male rats (approximately 3250 mg/kg bw/day). Although minor changes in clinical chemistry were also seen in female rats, some female rats (4/10) also exhibited liver nodules (diaphragmatic nodules) and small increases in liver weights. As no NOAEL could be established for female rats, a LOAEL of 4400 mg/kg bw/day was established. For male mice, a LOAEL at 9700 mg/kg bw/day was established, based on increased organ weights (liver, heart, kidney and lung) and decreased sperm counts in the cauda epididymis. Although female mice showed small changes in the length of dioestrus and pro-oestrus, the overall cycle length was unchanged. As biological significance of these changes was unclear, a NOAEL for female mice was established at 5 % (9400 mg/kg bw/day) (OECD, 2005; REACH).

Dermal

No data are available.

Inhalation

As properly conducted studies in animals are not available, there are no valid data on the effects of repeated inhalation exposure to the chemical. However, limited information is presented below to indicate that the chemical is likely to be of low toxicity following repeated inhalation exposure.

In a repeated dose toxicity study, SD male rats (10/dose) were exposed to the chemical through inhalation (whole body exposure) continuously at 20 mg/L for three, six, nine, and 26 days. Although initial exposure to the chemical produced a number of transient effects (lethargy, ataxia and intoxication, mild hepatic vacuolisation and changes to clinical chemistry parameters), animals adapted and appeared normal at the end of the study. Induction of metabolic tolerance to the chemical

was also indicated as it was noted that the levels of the chemical in the blood of animals exposed for 26 days were much lower than those exposed for shorter periods (REACH).

In another repeated dose toxicity study, the chemical was administered through inhalation at 0 or 6300 ppm (1 ppm = 1.92 mg/m³) to SD rats (10/sex/dose) for six hours/day, five days/week, for four weeks (total of 20 days exposure). Additional groups of animals (five/sex/dose) were also included in the study to determine reversibility of effects for a further four weeks following cessation of treatment. There were no treatment-related clinical signs of toxicity and there were also no gross pathological or histological changes reported of the major organs. Body weights, liver enzyme levels, haematology, and clinical chemistry parameters were otherwise normal (REACH).

Observation in humans

Long-term excessive consumption of alcoholic beverages is also associated with liver effects—fatty liver, alcoholic hepatitis, cell necrosis, fibrosis and cirrhosis (IARC, 1988).

Genotoxicity

Overall, the data indicate that the chemical has no mutagenic or genotoxic potential (OECD, 2005; REACH).

The results from numerous bacterial mutation assays of the chemical have generally been negative. A very weak positive effect of the chemical was found in an *Escherichia coli* DNA repair test but not in Ames tests with *Salmonella typhimurium* conducted by the same authors. In separate studies, there have been positive results reported in Ames tests, but only at concentrations of the chemical significantly greater than those specified in test guidelines. The chemical is therefore not considered mutagenic in bacteria.

The chemical has also been tested in several chromosome aberration assays. Many of these studies have limitations such as insufficient dose ranges and lack of metabolic activation. Accordingly, a weight of evidence approach is required to draw conclusions regarding clastogenic potential. No chromosome aberrations were found in testing with human lymphocyte cultures, lymphocyte cell lines, or Chinese hamster ovary (CHO) cells. Chromosome aberrations were detected in CHO cells but only in the presence of metabolic activation using plant microsomal extracts. Collectively, there is little evidence that the chemical is clastogenic in vitro. It has been considered that positive responses with high chemical concentrations may be an artefact, attributable to damage from high osmotic pressures.

The chemical has also been tested in cell mutation (mouse lymphoma) assays with negative results. A statistically significant increase in mutants was reported both in the presence and absence of metabolic activation in a mouse lymphoma assay designed to assess false positive results. However, the mutant frequencies remained low and the result was regarded as negative.

Several in vivo micronucleus assays have assessed the potential for the chemical to induce damage to chromosomes of erythroblasts. No effect was reported in rats when administered 5 % of the chemical (approximately 4 g/kg bw/day) in drinking water, or in mice at up to 40 % (approximately 31 g/kg bw/day). Chemical-related mortality was observed in the latter study. Marginally statistically significant increases in the incidence of micronucleated bone marrow erythrocytes were reported in rats fed for six weeks with a diet containing ethanol at 12–16 g/kg/day. Although there is very limited evidence that the chemical induces micronuclei in the bone marrow of rodents, the chemical has the potential to induce micronuclei in bone marrow erythrocytes at very high doses.

No chromosome aberrations were found in bone marrow or peripheral blood lymphocytes of rats receiving the chemical at up to 15.7 g/kg bw/day in drinking water. Similarly, no chromosome aberrations were found in the bone marrow of Chinese hamsters receiving the chemical in drinking water at up to 20 % for 12 weeks.

Results of dominant lethal assays with the chemical have been mixed. Interpreting the results has been confounded by inadequacies in methodologies, and using high ethanol doses often produced confounding toxicological effects. The most robust dominant lethal testing was identified as a collaborative inter-laboratory study conducted to OECD test guidelines. In this study, male mice were exposed via intubation to doses of the chemical at and below the maximally tolerated dose. No significant effects were reported.

Increased frequencies of chromosome aberrations have been reported in several studies of peripheral blood lymphocytes in alcoholics (IARC, 1998; IARC, 2010).

Carcinogenicity

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence in humans and experimental animals to establish carcinogenicity of alcohol consumption and ethanol, respectively. It was also concluded that there is sufficient evidence in experimental animals to establish carcinogenicity of acetaldehyde (major metabolite of ethanol). Consequently, IARC has classified that 'alcohol consumption is carcinogenic to humans (Group 1)' and that 'ethanol in alcoholic beverages is carcinogenic to humans (Group 1)'. This conclusion was supported by an analysis of the expanded human dataset that carcinogenic effects appeared independent of the type of alcoholic beverage (IARC, 2010; IARC, 2012).

As the use of the chemical in alcoholic beverages is not considered in this report, the above assessment of carcinogenicity of alcohol beverages may not be relevant to occupational exposure to the chemical or from using the chemical in consumer products (OECD, 2005). Furthermore, studies in animals conducted mostly through oral exposure at very high doses, exceeding the 'maximum tolerated dose', may be of little relevance when assessing risks associated with occupational exposure or using consumer products containing the chemical (OECD, 2005). Thus, classification is not considered appropriate.

Animal studies

In a similar fashion to studies of repeated dose toxicity, studies of carcinogenicity have been conducted in experimental animals, often with the aim of assessing risks from consuming alcoholic beverages. However, most of these early studies published between 1965 and 1987 have been criticised on methodological grounds such as the small numbers of animals used, the inadequate design of the experiments, the short exposure to ethanol, low doses of ethanol and the failure to measure ethanol intake and/or concentrations in the blood. Based on these studies, evidence for carcinogenicity of the chemical in experimental animals was concluded by IARC to be inadequate (IARC, 1988).

In subsequent reviews by IARC, studies of chemical exposures in animals (additional to those assessed by IARC in 1988) including studies of the modifying effects of the chemical on the activity of various carcinogens, were noted. In contrast to earlier conclusions in 1988, IARC has now determined that there is sufficient evidence to establish the carcinogenicity of the chemical in experimental animals. It was also concluded that there is sufficient evidence in experimental animals to establish the carcinogenicity of acetaldehyde, the primary metabolite of ethanol (IARC, 2010; IARC, 2012).

In mice, oral studies have been conducted with the chemical administered in drinking water, by gavage or in the diet. Doses ranged from 1–20 % of drinking water to a total of 30 % of total dietary calories. Exposure periods ranged from 4–104 weeks. Although the majority of studies failed to detect increases in tumour incidence, it was also noted that many studies were criticised on the basis of methodological shortcomings as stated above (IARC, 2010).

In one study, groups of 20 female ICR mice received 10 % of the chemical in drinking water for two months and then 15 % of the chemical in drinking water for 23 months. Beginning eight months after treatment, mammary gland tumours (papillary or medullary adenocarcinoma) were detected in 45 % (9/20) mice receiving the chemical compared with 0/20 control mice receiving the chemical in drinking water alone. The dose was estimated at 13.2 g/kg bw/day (IARC, 2010; IARC, 2012). In another long-term oral study, B6C3F$_1$ mice were exposed to 2.5 and 5 % of the chemical in drinking water (equivalent to 80–100 mg/day and 155–180 mg/day, respectively) for 104 weeks. This is equivalent to approximately 2.2 and 4.2 g/kg bw/day for both sexes. A dose-related trend of increased incidences of hepatocellular neoplasms was noted in males. Females showed no evidence of these effects. It was also noted that the maximum tolerated dose may have not been used in this study and that serum concentrations of the chemical were too low to measure (OECD, 2005; IARC, 2010; IARC, 2012).

As described by IARC (2010, 2012), several additional oral studies in rats have been conducted with the chemical administered in drinking water or the diet. Doses ranged from 1–10 % of drinking water to 3% of diet. Exposure periods ranged from 51–179 weeks. While the lack of measurement of blood ethanol concentrations was a common criticism of these studies, conflicting results were reported with respect to carcinogenicity of the chemical.

In a chronic multigenerational study, male and female SD rats and their offspring were administered the chemical in drinking water at 10 % concentration, starting at 39 weeks of age (breeders), seven days before mating or from birth (offspring) until death (last death at 179 weeks for offspring). Administration of the chemical resulted in a significant increase in the incidence of head and neck carcinomas (oral cavity, lips, tongue) in male and female breeders and male and female offspring; benign and

combined benign and malignant tumours of the forestomach in male breeders; and combined lymphomas and leukaemias in female breeders. Male breeders also exhibited an increased incidence of interstitial-cell adenomas of the testis and osteosarcomas of the head and other sites. Conclusions from this study are limited because of the single high dose, insufficient data reporting, and inconsistencies between conclusions and statistical analyses (OECD, 2005; IARC, 2010; IARC, 2012).

In another long term study, male and female SD rats were administered the chemical as a liquid diet at 1 and 3 % concentration for 104 weeks. The dose was estimated at 1–3 g/kg bw/day. Even though the body weights of the higher dose group were significantly reduced, the survival rates were not affected in any treatment group. Various non-neoplastic findings were noted—more significantly in the treatment groups than the control group. Although the incidence of all tumours was significantly reduced among females of treatment groups, a significant increase in pituitary tumours was noted among females in the high dose group compared with the control group. A significant increase in mammary gland fibromas, fibroadenomas and adenomas combined, was also noted in females in the low dose group. It was also noted that, considering the high rate of chemical metabolism in these rats, the chemical intake was relatively low and the concentrations of the chemical were not measured in the blood (OECD, 2005; IARC, 2010; IARC, 2012).

In a study to determine the effect of ethanol on vinyl chloride carcinogenesis, male SD rats received ethanol at 5 % concentration in drinking water for 130 weeks. Hepatocellular carcinomas (8/79 versus 1/80 control rats) and an increase in the incidence of hyperplastic liver nodules were noted in rats treated with the chemical. Treated animals also had pancreatic adenomas (18 %; 14/79), adrenal gland adenomas (18 %; 14/79), and pituitary adenomas (33 %; 26/79). While tumours of the pancreas or adrenal gland were found not in control rats, pituitary adenomas were noted in 8/80 control rats (IARC, 2010; IARC, 2012).

Other animal studies have been performed to determine whether ethanol modifies chemically-induced carcinogenesis. In these, known carcinogens were administered to animals orally with ethanol as a vehicle, or administered by different routes at various times with ethanol administered in drinking water or liquid diets. Some studies have been criticised because of methodological shortcomings. Positive results are reported in some studies whilst others report negative findings (IARC, 2010). Overall, increases in tumours (mostly in target organs characteristic of the carcinogens used) were observed in experiments in which ethanol was used as a vehicle for N-nitrosamines and 7,12-dimethylbenz[*a*]anthracene (DMBA). Similar results were obtained in some experiments, but not all, when ethanol was given to animals just before administration of the carcinogen or separately. There was no effect on carcinogenesis in most experiments when ethanol was given separately and after administration of the carcinogen, or when ethanol concentrations were low e.g. 5 %. The positive findings have been interpreted as indicating that ethanol may influence initiation of carcinogenesis; or influence mechanistic events such as entry of the carcinogen into target cells, intracellular metabolism or suppression of DNA repair. Competitive inhibition of hepatic metabolism of the carcinogen, allowing it to reach target organs, has also been indicated (IARC, 2010). A range of positive studies on co-carcinogenicity of the chemical with known carcinogens have also been published separately (IARC, 2012).

Human studies

Since the conclusion of a causal relationship between consumption of alcoholic beverages and carcinogenicity was published (IARC, 1988), a large number of additional epidemiological studies have reported on the association between alcohol consumption (containing ethanol and water as the two main components) and cancers at various sites (IARC, 2010; IARC, 2012). These indicate that regular alcoholic consumption is associated with an increased risk of malignant tumours of the oral cavity, pharynx (excluding the nasopharynx), larynx, oesophagus, liver, colorectum and female breast. An association between alcohol consumption and a small increased risk of cancer of the pancreas has also been recently noted (IARC, 2012). Consumption in excess of 10–40 g ethanol a day appears necessary before there is an appreciable increase in relative risk for cancer of oral cavity, pharynx, larynx and oesophagus (OECD, 2005). Daily consumption of 50 g ethanol was associated with a 2–3 fold increase in the risk of upper digestive tract tumours compared with non-drinkers. Similarly, daily consumption of 50 g ethanol was associated with relative risks for colorectal cancer and breast cancer of 1.4 and 1.5 respectively, compared with non-drinkers (IARC, 2010; IARC, 2012).

However, the evidence did not suggest that carcinogenicity is linked to the mutagenic effects of ethanol, acetaldehyde or other beverage constituents (OECD, 2005). The aetiology of cancers of the oral cavity, pharynx (excluding the nasopharynx), larynx and oesophagus is thought to be linked to persistent irritation, hyperplasia and finally tumour formation (OECD, 2005). The aetiology of liver cancer following alcoholic beverage consumption is commonly linked to cirrhosis, normally seen only following chronic intakes of greater than 80g ethanol per day (OECD, 2005). The risk for liver tumours was more difficult to estimate due to the confounding effects of cirrhosis and other liver diseases that often occur before the cancer becomes manifest and lead to reductions in alcohol intake in patients (IARC, 2010; IARC, 2012). The chemical has also been used in ready-to-use mouthwashes in a concentration up to 27 %. The safety of these preparations with respect to carcinogenic effect (increased risk of oral cancer) has been a source of controversy over decades (Lachenmeier DW, 2008; Gardini et al, 2012).

There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk of developing alcohol-related cancers, in particular of the oesophagus and the upper aerodigestive tract.

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. As results of inhalation studies showed no developmental toxicity from chemical exposures even at maternally toxic doses, it can be concluded that deliberate oral consumption of alcoholic beverages is required for any reproductive or developmental toxicity (OECD, 2005).

It has also been argued that many developmental toxicity studies investigated effects of high dose oral ethanol intake and often dosed animals well above the maximum limit of 1g/kg bw/day recommended in current OECD test guidelines. As ethanol represented a significant portion of daily caloric intake in these studies with consequent reductions in nutrient intake, malnutrition may be a confounding variable. Deprivation of nutrients during critical periods of gestation could also produce significant postnatal effects of its own (OECD, 2005).

Treatment of Swiss Webster male mice with the chemical at 10 or 25 % concentration of dietary calorie intake over seven weeks had no effect on fertility, on litter size or on pup weight. However, paternal bodyweights were lower at 25 % than at 10 % concentration. In a two-generation reproductive toxicity study, the chemical administered to CD-1 mice in drinking water at concentrations of 5, 10 and 15 % (20.7 g/kg bw/day at 15 %) for 105 weeks had no effect on fertility indices in P (parent) and F1 (first offspring) generations. Although F1 males exposed to the chemical at 15 % concentration showed a significantly decreased percentage in motile sperm, there was no effect on sperm concentration, percentage of abnormal sperm or percentage of tailless sperm. However, there was a significant decrease in testis, epididymis and seminal vesicle weights. Clinical signs as well as data on fertility effects in females were not evaluated (OECD, 2005; US EPA, 2001; REACH).

Treatment of male SD rats with the chemical at 2500 or 5000 mg/kg bw/day for three or nine weeks using gavage had no effect on fertility. However, an increase in foetal weights of offspring sired by treated males was noted (US EPA, 2001; OECD, 2005; REACH). The effect on fertility was also not reported in SD male rats exposed (gavage) to the chemical at either 2000 or 3000 mg/kg bw/day for nine weeks. This study did reveal higher incidences of runted pups in the resulting offspring at the highest exposure level of 3000 mg/kg bw/day. An effect on fertility was also not noted in male rats exposed to the chemical at 10000 or 16000 ppm (30400 mg/m^3) through inhalation for seven hours a day for six weeks. This level of exposure is associated with a blood alcohol concentration of 500 mg/L (0.05 %). Although an adverse effect on male fertility was noted in SD rats in another study that administered the chemical at 10 % in the diet (estimated at 7.2–14.4 g/kg bw/day) for 15 days before and during the mating period, this study was confounded by paternal toxicity manifested as ataxia, lethargy, and weight loss during the study period (OECD, 2005; US EPA, 2001; REACH).

A reproductive toxicity study in females has noted that the administration of the chemical at 5 % concentration (but not 2.5 %) for 50–55 days reduced bodyweight gain, increased the time to vaginal patency, the failure to begin oestrus cycles, ovaries containing only a single generation of corpora lutea, infantile vaginal and uterine epithelium, and reduced uterine and ovarian weight. The dose was estimated to be 8–12 to 12–14 g/kg/day at 2.5 and 5 % concentrations, respectively. A NOAEL of 8 g/kg bw/day was established for the study.

In another study, reduced weight gain, and reduced weight of the ovaries, uterus and fallopian tubes were noted in female Wistar rats treated with the chemical for 49 days at 5 % as a liquid diet (5.4–11.4g/kg bw/day) providing 36 % of the diet as ethanol-derived calories. Histological examination revealed differences in the appearance of the uterus, cervix and vagina of treated animals, and also an absence of developing follicles, corpus lutea and corpus haemorrhagica in the ovaries of the treated animals. Age for vaginal patency was also increased. Although irregular cycles and longer oestrous cycles were noted in another study in rats fed the chemical at 5 % in a liquid diet for 16 weeks, but not for 8 weeks, there were no adverse effects on fertility, litter size or neonatal bodyweight (OECD, 2005; US EPA, 2001; REACH).

In a developmental toxicity study, foetal weights were depressed and skeletal abnormalities were noted in all offspring of female mice treated pre- and post-gestation with the chemical in the diet at doses representing 15, 20, 25, and 30 % of caloric intake. Visceral abnormalities varying from 36 to 100% were also noted in the treatment groups. In another study, malformations were also significantly increased in mice by maternal diets containing 25 % or more of ethanol-derived calories. Malformations were also significantly increased by maternal diets containing 25 % or more of ethanol-derived calories in female C57BL mice exposed to the chemical at 17, 25 and 30 % of calories intake. These doses were calculated to be equivalent to 17, 29 and 28

g/kg bw/day. Litter weights were not affected by the treatment. A maternal as well as a developmental NOAEL of 17 g/kg bw/day was determined.

In another developmental toxicity study in CD-1 mice, the chemical was administered (gavage) at doses of 2.2, 3.6, 5.0, 6.4 and 7.8 g/kg bw/day on gestation days 8–14. Maternal toxicity (lethargy, staggered gait and laboured breathing) were seen from 3.6 g/kg bw/day. At 7.8 g/kg bw/day, all dams died. There were no significant dose-related adverse effects on foetuses even at doses associated with maternal toxicity. While the NOAEL for maternal toxicity was established as 2.2 g/kg bw/day, a NOAEL for developmental effects was reported at 6.4 g/kg bw/day (the highest dose for which developmental data could be obtained) (OECD, 2005). Rats treated with the chemical at 1g/kg bw/day (12.5 % in water) by gavage throughout gestation, and gestation plus lactation, showed impaired learning in both genders at nine weeks compared with controls, with impairment still evident in males at five months (OECD, 2005).

In another developmental toxicity study, female SD rats were fed a liquid diet containing the chemical at 15, 25, or 36 % of ethanol-derived calories from three weeks before mating to gestational day 21. These doses were equivalent to 5.2, 8.2, and 10.4 g/kg bw/day, respectively. Although there was no statistically significant difference in maternal weight gain between the treatment and control groups, there was a significant decrease in weight gain at the 8.2 g/kg bw/day dose, compared with other groups. A developmental NOAEL of 5.2 g/kg bw/day was established for this study, based on statistically significant changes in foetal growth (body weight and length) or skeletal ossification (at various sites). A developmental LOAEL of 8.2 g/kg bw/day was also established for this study, based on a delay in early development (statistically significant reduction in skeletal ossification of the ulna, radius, tibia and scapula) seen at 8.2 g ethanol/kg bw/day. In addition to a delay in early development, decreased foetal weight and length were also noted in the 10.4 g/kg bw/day treatment group. There were no skeletal malformations or variations (other than the delay in ossification) reported for any of the ethanol-treated groups (RAECH).

In the first of a series of inhalation developmental toxicity studies, groups of SD rats were exposed to the chemical at concentrations of 0, 10000, 16000 or 20000 ppm (equivalent to17, 29 and 28 g/kg bw) for seven hours a day throughout gestation from days1–9. Blood alcohol levels ranged from 0.02 to 0.03 mg/mL at 10000 ppm, 0.42 to 0.84 mg/mL at 16000 ppm and 1.48 to 1.93 mg/mL at 20000 ppm. The chemical induced severe maternal toxicity (complete narcosis, reduced food intake) at 20000 ppm, but dams also appeared hyperactive after exposures at the lower exposure levels. Foetal weights were slightly reduced at 16000 and 20000 ppm but the differences were not statistically significant. There were also no significant differences in incidences of external, visceral or skeletal malformations or variations at these doses. While a NOAEL for maternal toxicity was established as 16000 ppm (30400 mg/m³), a NOAEL of 20000 ppm (38000 mg/m³) was established for developmental toxicity (OECD, 2005; REACH).

Similar to the above inhalation study, experiments were conducted in SD rats with the chemical at doses of 0, 10000 and 16000 ppm where animals were allowed to have litters in order to assess behavioural effects in offspring. As litter size, birth weights, offspring survival, growth, and postnatal behaviour were unaffected, even at the highest tested dose, a developmental toxicity NOAEL of 16000 ppm, with an average blood alcohol level of 420 mg/L, was established (OECD, 2005).

Observations in humans

Effects of alcoholic beverages on reproduction in humans have been extensively reviewed. Alcohol consumption can interfere with both male and female reproductive function through effects on reproductive cells and adverse regulation of sex hormones. Ethanol is a recognised human teratogen. Multiple terms are used to describe a continuum of effects that result from prenatal exposure to ethanol. Foetal alcohol syndrome is the most common description of a collection of the most severe abnormalities linked with alcohol abuse. Abnormalities include pre- and/or postnatal growth retardation, characteristic craniofacial dysmorphology, mental retardation, cardiac septal defects, joint abnormalities and additional alterations in multiple organs and systems (IARC, 2010; IARC, 2012).

Risk Characterisation

Critical Health Effects

While exposure to the chemical through consuming alcoholic beverages is associated with an increased risk of carcinogenicity and reproductive and developmental toxicity, these risks increase in a dose-dependent manner and are not considered relevant at doses relating to occupational exposure and using consumer products containing the substance such as mouthwash.

Therefore the critical health effect for risk characterisation from industrial use of the chemical is a local effect: eye irritation.

Public Risk Characterisation

Considering the range of domestic and cosmetic products that may contain this chemical, the main route of public exposure is expected to be through the skin and eyes, and inhalation from products applied as cosmetics and using domestic products.

Although the concentration of the chemical for cosmetic uses is not known (see **Import, manufacture and use**), considering reported uses of the chemical for cosmetic purposes, reported information indicated a low concern with respect to eye irritation. Even though a much higher concentration of the chemical has been stated to be used for domestic uses (up to 100 %), provided that normal precautions are taken to avoid eye contact, the risk from the use of domestic products is not considered to be unreasonable. Spray application of products containing the chemical may result in reversible eye irritation, although the likelihood is low. The effects are likely to be slight and reversible.

Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical may pose an unreasonable risk to workers, particularly at high concentrations, unless adequate control measures to minimise ocular exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

The data available support an amendment to the hazard classification in HSIS (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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral and ocular exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- 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 assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

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

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

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace*

hazardous chemicals—Code of practice, respectively. These codes of practice are available from the Safe Work Australia website.

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

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