Benzeneethanol: 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.

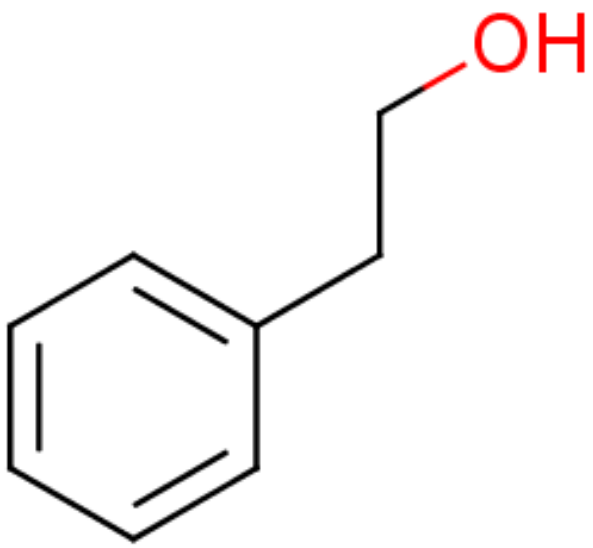
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	phenylethyl alcohol 2-phenylethanol 2-phenylethan-1-ol benzyl methanol ß-hydroxyethylbenzene
Structural Formula	
Molecular Formula	C8H10O
Molecular Weight (g/mol)	122.17
Appearance and Odour (where available)	Colourless, viscous liquid with a floral odour.
SMILES	c1(CCO)ccccc1

Import, Manufacture and Use

Australian

The chemical has reported domestic use in glass cleaners.

It has uses in rubber compounds and surface refinishing products for marine applications.

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 US National Library of Medicine's Hazardous Substances Data Bank (HSDB); Cosmetic Ingredient Review (CIR, 1990; CIR, 2008) and the United States Environmental Protection Agency (USEPA) Screening-Level Hazard Characterization (2010).

Benzeneethanol has reported cosmetic use as a fragrance ingredient, preservative and solvent in shampoos, cleansing products, eye makeup, eye makeup removers, skin care products and hair care products. It is listed in the International Fragrance Association (IFRA) Transparency List. The reported frequency of use in the USA is 63 (Personal Care Products Council, 2011). Reported concentrations in cosmetic products are typically below 1 % (up to 0.5 % in soap, 0.2 % in creams and lotions and 0.8 % in eye make up products). Concentrations up to 2 % in perfumes and 10 % in deodorants have been reported (CIR, 1990; CIR, 2008; US Household Products Database).

The chemical has reported domestic use with concentrations up to 15 % (US Household Products Database), including:

- in cleaning and washing products;
- as an odour agent;
- in paints, lacquers and varnishes;
- in surface treatment;
- in paper products;
- in room and car deodorisers;
- in polishes and waxes; and
- in washing and cleaning products.

The chemical has reported commercial use, including:

- in softeners; and
- as an absorbent.

The chemical has reported site-limited use, including chemical product and preparation manufacturing in addition to other basic organic chemical manufacturing.

The chemical has non-industrial use as a flavouring agent (JECFA 2002), feed additive for animals (EFSA 2012), in non-agricultural pesticides, and in pharmaceutical products. It has been used in 0.5 % as an antibacterial agent in ophthalmic solutions (HSDB).

Benzeneethanol occurs naturally in the environment and is produced by microorganisms, plants and animals. It has been found as the free alcohol or esterified in a number of natural essential oils, and in food, spices, and tobacco (CIR, 1990).

The chemical is an ingredient in e-cigarette liquids (NICNAS, 2019).

The chemical was included in the High Production Volume (HPV) Challenge Program, a voluntary initiative aimed at providing information on chemicals manufactured in or imported into the USA in quantities greater than one million pounds per year. The USEPA reported that aggregated production and/or import volume in the Unites States was 1–10 million pounds in 2006 (USEPA, 2010). This substance is manufactured and/or imported in the European Economic Area in 1000–10000 tonnes per year (REACH).

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Benzeneethanol is a naturally-occurring chemical found in natural products and used as a flavouring agent. The Joint Food and Agriculture Organisation/World Health Organisation (FAO/WHO) Expert Committee on Food Additives (JECFA) assessed benzeneethanol and other related flavouring agents and concluded that none of the chemicals would present a safety concern at current estimated levels of intake. The JECFA did not require any toxicity data for benzeneethanol and most of the chemicals in this group because they were “predicted to be metabolized to innocuous agents and the estimated intakes were below the human intake threshold associated with the relevant structural class” (JECFA, 2002). The chemical was assessed by the European Food Safety Authority (EFSA) for use in the feed of food-producing animals and the maximum safe concentration was calculated to be 1–1.5 mg/kg feed (EFSA, 2012).

Toxicokinetics

The toxicokinetics of benzeneethanol has been investigated in humans, rats, rabbits and dogs following single or repeated applications using the oral and dermal exposure routes. The chemical is rapidly absorbed and oxidised to phenylacetic acid, which is conjugated and excreted primarily in the urine of mammals. In humans, it is excreted in urine as the conjugate phenylacetylglutamine (JECFA, 2002; EFSA 2012).

In a human study using radiolabelled benzeneethanol, ^{14}C-2-phenylethanol was applied topically to two men at a nominal dose level of 0.1 mg/cm^2 in ethanolic solution. The application area was washed 6 hours after application. Radioactivity was only detected in the urine during the 48 hours following application with most of it appearing within 12 hours. No radioactivity was detected in the faeces. The test substance was rapidly absorbed and excreted during the first 4 hr reaching the peak of 13.8 ng/mL at 1.5 hours. During 5 days after topical application of the radiolabelled benzeneethanol, a mean of 7.55 % of the dose, measured as the total detected in urine and faeces, was absorbed through the skin. The major metabolite detected was phenylacetyl glutamine (4.1 % of the dose) and the second (2.7 % of the dose) was a conjugate (glucuronide or ethereal sulphate). Most of the dose (ca. 90 %) was lost from the surface of the skin due to evaporation (CIR, 1990; REACH).

Studies in animals found similar results with rapid absorption of the chemical and excretion in the urine. The major metabolite was found to be phenylacetic acid (CIR, 1990: REACH).

A rat study with topical application of radiolabelled benzeneethanol found radioactivity in the skin, fat and pancreas following a 6 hour application. Radioactivity was detected in the foetuses of dams that were administered 10 doses of the radiolabelled chemical at either 0.14 or 0.7 mL/kg bw for an unspecified dosing period (CIR, 1990).

Acute Toxicity

Oral

Based on the reported oral median lethal dose (LD50) 1609 mg/kg bw in rats, the chemical has moderate oral toxicity, warranting hazard classification (see **Recommendation** section).

In an acute oral toxicity study similar to OECD Test Guideline (TG) 401 and compliant with good laboratory practice (GLP), Sprague-Dawley (SD) rats (5/sex/dose) were treated with the chemical and the LD50 was reported to be 1609 mg/kg bw. Reported signs of toxicity included diarrhoea, hypersensitivity, tremors, wheezing, prostration, abnormal gait and body drop.

The following oral LD50 values were reported in studies with limited details (USEPA, 2002; CIR, 1990):

- 650 mg/kg bw in male rats and 1430 mg/kg bw in female rats, degeneration of the liver and kidneys was observed;
- 1500 mg/kg bw in male Wistar rats;
- 1790 mg/kg bw in male and female Osborne-Mendel rats;
- 2509 mg/kg bw in Carworth-Wistar rats;
- 2540 mg/kg bw in rats;
- 800–1500 mg/kg bw in mice;
- 2540 mg/kg bw mg/kg bw in mice;
- 400–800 mg/kg bw in guinea pigs; and
- 2540 mg/kg bw in guinea pigs.

Dilute solutions of benzeneethanol were administered to mice to investigate narcotic effects and to rats to evaluate potential toxicity. No toxic effects were observed in the rats. However, intoxicating effects were found in the mice (CIR, 1990).

Dermal

The chemical has low toxicity based on results from animal tests following dermal exposure. LD50 values were reported in rats (>5000 mg/kg bw), rabbits (790–2535 mg/kg bw) and guinea pigs (6010–12020 mg/kg bw) (CIR 1990, USEPA 2002; REACH).

In a dermal acute toxicity study similar to OECD TG 402 and compliant with GLP, New Zealand White (NZW) rabbits (4/sex/group) were administered benzeneethanol on abraded or intact skin under occlusive conditions for 24 hours and subsequently observed for 14 days. The LD50 was determined to be 2535 mg/kg bw. Signs of toxicity included erythema, body drop, tremors, partial posterior paralysis, excessive grinding of the teeth and diarrhoea (REACH); USEPA, 2002).

In a dermal acute toxicity study similar to OECD TG 402 and compliant with GLP, rats were administered the chemical (n=10). The LD50 was reported to be >5000 mg/kg bw (USEPA, 2002).

The chemical was administered dermally to male NZW rabbits (4/group) at unspecified doses to intact skin under occlusion for 24 h and with 14 days observation. The LD50 was reported to be 805 mg/kg bw (USEPA, 2010).

The following dermal median lethal dose (LD50) values were reported in studies with limited details (USEPA, 2002; CIR, 1990):

- 790 mg/kg bw in rabbits;
- 5000 mg/kg bw in guinea pigs; and
- 5–10 mL/kg bw in guinea pigs (equivalent to 6000–12000 mg/kg bw).

Inhalation

The chemical has low toxicity based on results from a rat study following inhalation exposure. The reported median lethal concentration (LC50) was >4.63 mg/L in rats.

In an acute toxic class inhalation toxicity study and compliant with GLP, SD rats (25/sex) were exposed (whole body) to the chemical at a nominal concentration of 4.63 mg/L for 4 hours and observed for 14 days. No treatment-related effects were reported. The LC50 was determined to be >4.63 mg/L (REACH; USEPA, 2002).

Corrosion / Irritation

Skin Irritation

Based on most of the available animal and human data (see **Irritation: Observation in humans)**, benzeneethanol is not considered to be a skin irritant, although the chemical was found to be irritating if applied repeatedly to skin for 24 hours (see **Reproductive & Developmental Toxicity section**).

In a skin irritation study similar to OECD TG 404 and compliant with GLP, 4 female NZW rabbits were treated with benzeneethanol for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48, 72 and 7 hours after patch removal. The responses declined gradually and disappeared after 168 hours. The following mean scores were reported at 24, 48 and 72 hours: 1, 0.75 and 0.5 for erythema and 0.5, 0.25 and 0.25 for oedema respectively (maximum score of 4) (REACH).

In a skin irritation study similar to OECD TG 404, 3 female NZW rabbits were treated with benzeneethanol for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48, 72 and 168 hours after patch removal. The following mean scores were reported at 24, 48 and 72 hours: 2, 1.3, 1.3 and 0.33 for erythema and 0.7, 0.7, 0.7 and 0 for oedema respectively (maximum score of 4). Erythema was not reversible for one of the animals within 7 days (REACH).

The chemical was not found to be irritating in other studies with limited reported details and/or using non-guideline approaches in rabbits, guinea pigs and miniature swine (CIR, 1990; REACH).

Eye Irritation

Based on the available data, the chemical can cause serious eye damage, warranting hazard classification (see **Recommendation** section).

In an eye irritation study in NZW rabbits with limited reported details, the test substance was instilled in the eyes of rabbits and found to cause corneal necrosis (REACH).

A 0.005 mL dose of the pure chemical or a 0.5 mL dose of 5 or 15 % benzeneethanol in propylene glycol was found to cause severe corneal irritation and iritis following administration to rabbit eyes (CIR, 1990).

Irritation of the conjunctiva and transient clouding of the cornea were observed following the installation of the chemical (1 % solution) into rabbit eyes (CIR, 1990).

Dilute solutions of the chemical were not found to be irritating when administered to rabbit eyes in a number of studies. Instillation of the chemical at concentrations up to 2 % in saline induced loss of touch response in the cornea of rabbits. No ocular redness, discharge, or other sign of irritation were observed when two drops of 0.3 % benzeneethanol in saline solution were instilled into the left eyes of two rabbits three times a day, five days a week for 2 weeks. Ophthalmic preparations containing the chemical as a preservative were irritating to rabbit eyes. An eye makeup remover containing 0.05 % benzeneethanol was instilled in the conjunctival sac of one eye of 9 female NZW rabbits at a dose of 0.1 mL and was not found to be irritating (CIR, 1990).

Observation in humans

The chemical was not found to be irritating to the skin in human studies. However, dilute solutions cause eye irritation in humans.

Benzeneethanol was applied to the forearms of 20 male and female subjects, and the sites were covered with adhesive bandages for 24 h. No positive irritation reactions were observed at the applications sites over 5 days following the exposure. A 32 % solution of the chemical in acetone was applied via patches for 48 hours to the backs of 50 male subjects with no known allergic reactions. Skin irritation was not observed in the 30 minute period following patch removal (CIR, 1990).

Benzeneethanol (0.5 % in 0.9 % saline) caused a smarting sensation and slight conjunctival hyperaemia when applied as eye drops to 3 of 4 patients. A 0.75 % solution of the chemical was irritating to the human eye. Another source reported that concentrations of the chemical greater than 1 g/L in eye drops may be irritating to the human eye (CIR, 1990).

The use of the chemical and benzalkonium chloride as preservatives in a 2 % disodium cromoglycate nasal spray induced a chemical rhinitis (CIR, 1990).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser based on an LLNA study and clinical studies.

In a local lymph node assay (LLNA) performed in accordance with OECD TG 429 and compliant with GLP, female CBA mice (4/dose) received topical applications of 2.5, 5, 10, 25 or 50 % w/v benzeneethanol in 25 % ethanol/ 75 % diethylphthlate. The reported stimulation indices (SI) were 1.06, 1.01, 0.87, 0.95 and 0.84 for concentrations of 2.5, 5, 10, 25 or 50 % respectively. The chemical was not considered to be a skin sensitiser under the conditions of the test. As all SI values were below 3, the estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value could not be determined (REACH).

Observation in humans

Observations in humans support the conclusion that the chemical is not a skin sensitiser.

The EU Scientific Committee on Consumer Safety (SCCS) categorised benzeneethanol as a possible contact allergen based on very limited clinical information. One study identified 1 (0.6 %) positive reactions among 179 patients using a 25 % preparation of the chemical. In a dose-finding pilot study, no positive reaction was found when 100 consecutive patients were tested with 1 % of the chemical in petrolatum (SCCS, 2012).

In a repeated insult patch test (RIPT) study using 8 % benzeneethanol in diethyl phthalate, 108 subjects were exposed to the chemical. The negative control was a patch containing 20 % ethylene brassylate in diethyl phthalate, and the vehicle control was diethyl phthalate. Nine 24 h occlusive induction patches per test sample were applied to the upper arm, and one 24 h occlusive challenge patch was applied per test sample to the lower back of participants. The challenge patch sites were observed at 48 and 96 h. No evidence of skin sensitisation was observed (CIR, 1990).

The skin sensitisation potential of benzeneethanol was evaluated in 25 subjects. The induction phase involved applying a patch containing 1.0 mL of a 5 % sodium lauryl sulfate (SLS) solution to the skin for 24 h to produce a moderate inflammatory reaction and make the skin more permeable to the chemical. After removal of this patch, a patch containing 8 % benzeneethanol was applied for 48 h to the same site. The SLS and benzeneethanol patches were alternated for a total of five exposures each over a 15-day period. Following a 10-day non-treatment period, a 10 % SLS solution was applied to an untreated site for 1 h. A 48 h 8 % benzeneethanol challenge patch was subsequently applied to the same new site. The site was scored at patch removal and each day for two further days. There were no reported positive reactions (CIR, 1990).

An eye makeup remover containing 0.05 % benzeneethanol was tested in a repeat insult patch test with 54 male and 101 female volunteers and a use test with 53 female volunteers. There were no reported allergic responses (CIR, 1990).

Repeated Dose Toxicity

Oral

Based on limited data, the chemical has low toxicity following repeated oral exposure.

Rats were fed diets containing benzeneethanol at 62.5–2000 mg/kg bw/day for 14 days. No adverse effects were observed (CIR, 1990).

In a liver function study, male rats (number and species unspecified) were administered 51 mg/kg bw/day benzeneethanol orally for 4 months, resulting in changes in activity for some liver enzymes. The concentrations of blood serum proteins were slightly lower following treatment and galactose utilisation by the liver was greater. Few or no signs of toxicity were observed (CIR, 1990; USEPA, 2002).

Another oral study was summarised in a USEPA document and considered "not reliable" (USEPA, 2002). The developmental toxicity studies in rats and rabbits indicate that there is little maternal toxicity under the conditions of the studies at low to moderate doses, apart from one rat study, following subacute oral exposures to benzeneethanol (see the **Developmental Toxicity** section for more information).

Dermal

Based on the results from a 90-day study in rats, the chemical has low toxicity following repeated dermal exposure.

In a subchronic study, the chemical was applied once a day by rubbing it on the shaved backs of Charles River Cd rats (15/sex/group) at daily doses of 0.25, 0.50, 1,00, and 2.00 mL/kg (equivalent to 255, 510, 1020 or 2040 mg/kg bw/day, based on density = 1.0202 g/cm^3) for 90 days. No clinical abnormalities or deaths were observed during the treatment period. Clinical chemistry and urinary analyses did not show any significant changes. Microscopic examination of animals treated at the highest dose (2040 mg/kg bw/day) showed no treatment-related effects compared to control animals. Body weights in males and females decreased in a dose-dependent manner, and these decreases were statistically significant (8–11 %) at the two highest doses. There was a statistically significant decrease in the haemoglobin concentration and leukocyte count in males at the highest dose (2040 mg/kg bw/day). Absolute and relative liver weights were decreased in males in the 1020 mg/kg bw/day

group but not the highest dose. Relative liver weight at all doses among females, brain, kidney and gonad weight for both sexes in the highest treatment group were significantly increased. The NOAEL was determined to be 0.5 mL/kg bw/day (equivalent to 510 mg/kg bw/day) based on significant reductions in body weight and haematological effects in males and changes in organ weights for both sexes at higher treatment levels (REACH).

A 3 mL/kg bw/day dose (equivalent to 3061 mg/kg bw/day, based on density = 1.0202 g/cm³) of benzeneethanol was applied daily to the skin of 2 rats for up to 28 days. One of the rats died after 7 days of treatment. No other information was available (CIR, 1990).

Inhalation

No data are available.

Genotoxicity

The chemical is not considered to be genotoxic. Mainly negative results were reported in the following in vitro studies investigating genotoxicity (REACH; CIR, 1990; USEPA, 2002):

- negative results in a bacterial reverse mutation assay in *Salmonella typhimurium* TA1535, TA1537, TA98, and TA100 with or without metabolic activation in the Ames test conducted as a spot test with 3 µmol/plate of the chemical;
- negative results in a bacterial reverse mutation assay in *S. typhimurium* TA1535, TA1537, TA98, and TA100 with or without metabolic activation, at concentrations up to 5000 µg/plate;
- negative results in *Escherichia coli* DNA-polymerase-deficient assay system without metabolic activation;
- negative results in a thymidine kinase gene mutation test in L5178Y mouse lymphoma cells at 76.25–1220 µg/mL with or without metabolic activation;
- negative results in a sister chromatid exchange assay in human lymphocytes exposed to the chemical at concentrations of 0.1–10 mM;
- the chemical (0.25 % in ethanol) inhibited the repair of radiation-induced single-strand breaks in the DNA of *E. coli*; and
- negative in a chromosome aberration assay in human lymphocytes exposed up to 10 mM (1220 µg/mL) benzeneethanol, with or without metabolic activation using different exposure times and S9 concentrations.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity

There are no data on reproductive toxicity studies. A 90-day dermal repeated dose toxicity study (see **Repeated dose toxicity: dermal**) found no evidence of tissue alterations in testes, epididymides or ovaries in the highest dose group (2040 mg/kg bw/day). Gonad weight for rats of both sexes treated with benzeneethanol at the highest dose were significantly increased (REACH).

Based on the weight of evidence from a number of developmental toxicity studies, the chemical is not considered to cause specific developmental toxicity. Developmental effects were mostly observed secondary to maternal toxicity. Developmental delays were also observed at doses in the absence of overt maternal toxicity. These effects were subsequently found to resolve over time in a study that examined the reversibility of developmental delays by comparing effects observed in Caesarean-delivered foetuses at gestation day (GD) 20 in one series of treatments with those observed in a second series of treatments

where dams were allowed to have their litters naturally and pups were allowed to live three weeks after birth. In this study developmental effects observed in the foetuses were found to be fully reversible. Therefore, it appears that the similar developmental delays observed in the other studies are likely to be secondary to maternal toxicity.

Oral studies

In a prenatal toxicity study similar to OECD TG 414, pregnant Long-Evans rats (n=19) were dosed with aqueous suspensions of benzeneethanol at 4.3 (7/19), 43 (7/19), and 432 (5/19) mg/kg bw/day by gavage on gestation days (GD) 6–15. Dams were sacrificed on GD 20 and the foetuses examined. Severe maternal intoxication was observed at 432 mg/kg bw/day. No symptoms were observed in dams at lower doses. Mortality or malformations were observed in the foetuses at all doses and was dose-related (100 %, 97 % and 55 % in the high-, mid- and low-dose groups respectively). High-dose group pups had malformed eyes and limbs, hydronephrosis, and limb defects. Pups in the low-dose group had eye defects and hydronephrosis. Reduced ossification was observed in the skull, limbs, vertebrae, sternum, rib, or tail of treatment groups. Intrauterine growth retardation occurred in both the low- and high-dose groups (average pup weight and crown-rump length were decreased on a per litter basis, and numbers of live grossly runt pups were greater). Embryolethality was not observed in the high-dose group; however, the foetal death rate in the mid-dose group was significantly increased compared with the controls. The maternal no observed adverse effect level (NOAEL) was 43 mg/kg bw/day based on intoxication and the lowest observed adverse effect level (LOAEL) for foetal effects (malformations, reduced live litter size) was 4.3 mg/kg bw/day (CIR, 1990; USEPA, 2002; REACH).

In a dose range finding pre-natal developmental toxicity study compliant with GLP, benzeneethanol was administered by oral gavage to time-mated NZW rabbits (6/dose) at doses of 0, 4.3, 43, 200 and 300 mg/kg bw/day, from day 6 to day 28 post-coitum, inclusive. All of the animals in the highest dose group were terminated by day 12 post-coitum due to severe toxic effects including no food consumption and marked body weight loss. At 200 mg/kg bw/day, maternal toxic effects included marked reduction in food consumption and significant body weight loss followed by statistically reduced body weight gain over the entire treatment period. Based on reduced food consumption and body weight loss, the maternal NOAEL for benzeneethanol was determined to be 43 mg/kg bw/day. Developmental effects including increased post-implantation loss were observed in the groups treated with 43 and 200 mg/kg bw/day and reduced foetal weights at 200 mg/kg bw/day but these effects could not be evaluated because of small numbers of animals were used in this dose range finding study (REACH).

In a prenatal toxicity study compliant with GLP, benzeneethanol was administered by oral gavage to time-mated NZW rabbits (22/dose) at doses of 0, 15, 50, 150 mg/kg bw/day from day 6 to day 28 post-coitum, inclusive. Treatment at the highest dose resulted in reduced body weight and reduced weight gain in the pregnant rabbits. Complete recovery was not observed and mean foetal body weights were also reduced at the high dose. At this dose, mean combined foetal body weight was 10 % lower in males and females, the same dose at which lower maternal body weight gain from start of treatment until the end of pregnancy was also noted. In the high dose group, skeletal variations and malformations were observed. Maternal and developmental NOAELs were established at 50 mg/kg bw/day, based on the effects on maternal body weight gain and food intake, foetal body weight and skeletal malformation observed at 150 mg/kg bw/day (REACH).

In a prenatal toxicity study similar to OECD TG 414 and reported to be compliant with GLP, pregnant CrL: COBS CD(SD)BR rats (number not specified) were administered 1000, 3000, or 10000 ppm) microencapsulated benzeneethanol in feed on GD 6–15 (measured intake was 83, 266 and 799 mg/kg bw/day. The rats were sacrificed on GD 20 and the foetuses examined. Reduced maternal feed consumption and slight weight loss in dams were observed in the high-dose group only during the first 2 days of treatment. Treatment had no effect on embryo-foetal development and morphology; incidence, type, and distribution of malformations, anomalies, and skeletal variants in treated and control foetuses were comparable. There was an increased incidence of incomplete ossification in the high-dose group only. Treatment did not have detrimental effects on litter size, embryo/foetal loss, litter weight, mean foetal weight, or sex ratio. Maternal and developmental no observed effect levels (NOEL) were 10000 ppm (799 g/kg bw/day), the highest dose tested (CIR, 1990; USEPA, 2002).

In a prenatal toxicity study, pregnant rats were orally administered benzeneethanol in sunflower oil at 508 mg/kg bw/day on either GD 4 or GD10–12. Dams were sacrificed on GD 20 and the foetuses examined. No differences in size or number of foetuses and no developmental anomalies were observed in the treated groups. Embryos from the rats treated on days 10–12 of pregnancy were examined histologically. The size of the ossification sites at the extremities of the foetuses were smaller than those of the controls and some of the ossification sites were missing in 10–15 % of the foetuses. Sagittal sections were examined; no abnormalities were observed in palate structure, eyes, brain, or internal organs. No maternal data were reported (CIR, 1990; USEPA, 2002).

Dermal studies

In a combined dermal developmental and perinatal/postnatal reproduction toxicity study compliant with GLP, benzeneethanol was applied to the skin of two series of pregnant Crl:CD(SD) rats (40/dose) at 0, 0.14, 0.43 and 1.40 mL/kg bw/day (equivalent to 0, 143, 439 and 1428 mg/kg bw/day based on density = 1.0202 g/cm³), on GD7–20. Foetal and litter parameters were assessed in one series of animals on GD 21 while mothers from the second series were allowed to deliver their litters normally. Maternal toxicity (mortality, decreased food consumption and body weight) was observed at the highest dose (1428 mg/kg bw/day) and treatment of these groups ceased on GD15. Maternal dosages of mid- and high-dose levels caused reductions in foetal weight in the Caesarean-delivered foetuses with corresponding delays in foetal skeletal ossification and an increased incidence of cervical ribs. In contrast, pups from litters that had been delivered normally showed no evidence of these skeletal effects three weeks after birth, demonstrating that these effects were fully reversible. Reduction of pup body weights were also recorded for the high dose group throughout the post-partum period. The NOAEL for maternal and developmental toxicity was 439 mg/kg bw/day because the developmental delays and skeletal variations observed in the Caesarean-delivered foetuses were shown to be reversible (REACH).

In a prenatal toxicity study compliant with GLP, benzeneethanol was applied to the skin of pregnant CrL: COBS CD(SD)BR rats on GD 6–15 at doses of 0.14 (35 animals), 0.43 (25 animals) and 1.40 mL/kg (35 animals) (equivalent to 143, 439 and 1428 mg/kg bw/day, based on density = 1.0202 g/cm³). Dams were sacrificed on GD 20 and the foetuses examined. Severe maternal toxicity was observed at the highest dose including death of three of the dams, suppression of food intake, reduced growth rate and clinical signs of marked toxicity (decreased motor activity, impaired/lost righting reflex, ataxia, moderate excess salivation). Total resorption was seen for 5 of 23 litters, and 50 % or more embryo/foetal wastage in an additional 4 of 18 litters. However, 7 of 18 dams carrying to term had less than 10 % early resorptions. Morphological abnormalities observed in foetuses in the high-dose group including soft tissue and skeletal changes and incomplete ossification. No clear evidence of adverse treatment-related effects on parent and litter parameters was observed in the mid-dose group. Although the number of foetuses with soft tissue structural changes was greater than in the controls, there was no obvious pattern to the changes. The number of foetuses with moderate degrees of reduced ossification and with cervical rib(s) was significantly less than in the high-dose group, but was significantly greater than in the controls. At the low dose, there was no evidence of maternal toxicity or adverse effects on litter parameters. Although the incidence of structural changes was slightly greater in the rats treated at this dose compared with controls, the incidence and distribution of such changes were not conclusively associated with treatment. The lowest treatment level was associated with only equivocal evidence of effects on foetal skeletal development, but these could be seen as part of a dose dependent trend. The maternal NOAEL was 439 mg/kg bw/day based on mortality. The NOAEL for developmental toxicity was 143 mg/kg/day based on skeletal variations and delayed skeletal ossification (CIR, 1990; USEPA, 2002; REACH).

Another study was conducted under the same experimental conditions (8/dose) using different doses to better define the maternal and developmental NOAELs. The doses used were 0.07, 0.14, 0.28, 0.43 and 0.70 mL/kg (equivalent to 71, 143, 286, 439 and 714 mg/kg bw/day, based on density = 1.0202 g/cm³). Signs of dose-dependent dermal irritation was observed in all dams. Treatment did not reduce average maternal body weight, body weight gain, average maternal feed consumption or feed utilisation values in a consistent dose-dependent pattern. There were no treatment-related effects on average number of corpora lutea, implantations, litter sizes, or resorptions, average percentages of resorbed conceptuses and live male foetuses per litter. Dose-dependent decreases were observed in the litter averages for specific foetal ossification sites in all treatment groups, live foetal body weights were decreased significantly in litters from dams dosed at ≥143 mg/kg bw/day. The incidence of foetuses with cervical ribs was increased significantly only in the 714 mg/kg bw/day group litters. Apart from the increased incidence of foetuses with cervical ribs at the highest dose, all other foetal alternations were considered reversible delays in ossification. The maternal NOAEL (excluding local irritation at the treatment site) was 714 mg/kg bw/day. The foetal NOAEL was 71 mg/kg bw/day based on equivocal evidence of decreased foetal weights and the cervical rib incidence. (CIR, 1990; USEPA, 2002; REACH).

Other Health Effects

Neurotoxicity

The chemical is considered to be a more potent anaesthetic than benzyl alcohol. Following intraperitoneal or subcutaneous injection into mice in several studies, benzeneethanol caused muscular weakness and incoordination, exophthalmos, coma and death (HSDB; CIR, 1990).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is the potential to cause serious eye damage. The chemical can also cause systemic acute toxicity from oral exposure.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products overseas at concentrations up to 10 %. The chemical is reported to be used in glass cleaners in Australia but information on concentration is not available. However, benzeneethanol is reported to be used in domestic products up to 15 %. The public could be exposed to the chemical through use of these products. However, given the low concentrations typically used in cosmetics, particularly in products with potential eye contact and the normal precautions taken to avoid eye contact with domestic products, the chemical is not considered to pose an unreasonable risk to public health.

Although the chemical has reported use in e-cigarettes, due to lack of data suitable for assessing the inhalation risk (NICNAS, 2019), e-cigarette use has not been assessed in this report. NICNAS will continue to monitor for relevant toxicological data.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might 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 ocular exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

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

NICNAS Recommendation

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

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)

[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 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 that could minimise the risk include, but are not limited to:

- 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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