Benzaldehyde: Human health tier II assessment

01 July 2016

CAS Number: 100-52-7

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.

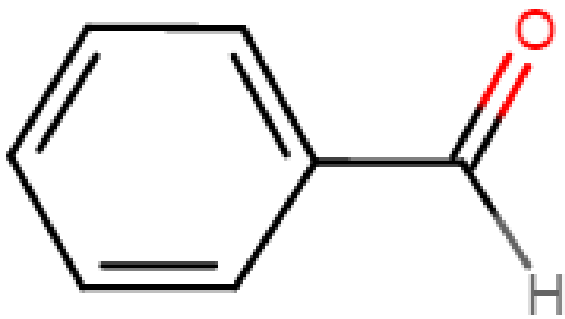
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	benzene carbaldehyde benzenecarbonal phenylmethanal benzenecarboxaldehyde benzoic aldehyde
Structural Formula	
Molecular Formula	C7H6O
Molecular Weight (g/mol)	106.12
Appearance and Odour (where available)	Colourless or yellow liquid with an almond-like odour.
SMILES	c1(C=O)ccccc1

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 as a fragrance ingredient;
- domestic use in home care applications;
- commercial use as a plastic additive; and
- site-limited use as an intermediate.

The total volume in introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was 1–10 tonnes.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; 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), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic uses including:

- as a denaturant;
- in solvents (oils, resins, cellulose ethers); and
- in perfumes and fragrances.

The chemical has been reported to be used in the EU in only seven cosmetic products, with a maximum reported concentration of use of 0.5 % in perfumes (CIR, 2006).

The chemical has reported domestic uses including in:

- adhesives (binding) agents;
- cleaning/washing agents;
- paints, lacquers, varnishes and various coatings;
- surface treatment;
- corrosion inhibitors;
- fillers; and
- odour agents.

The chemical has reported commercial uses including in:

- absorbents and adsorbents;
- construction materials;
- lubricants and additives;
- process regulators; and
- fabricated metal products, except machinery and equipment.

The chemical has reported site-limited use as an intermediate to synthesise other substances.

The chemical has reported non-industrial uses including in:

- pharmaceuticals;
- non-agricultural pesticides and preservatives; and
- flavourings and nutrients for food and/or foodstuffs.

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 classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R22 (Acute toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

The chemical has an exposure standard of 5 mg/m^3 time weighted average (TWA) in Bulgaria, Hungary, Latvia and Russia; 10 mg/m^3 in Poland; and 2 ppm in the USA.

Short-term exposure limits (STEL) of 4 ppm in the USA and Canada; 10 mg/m^3 in Hungary; and 40 mg/m^3 in Poland have been reported.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed via the respiratory and gastrointestinal tracts and also through intact skin. After absorption, the chemical is metabolised primarily by the liver; and/or enzymatic oxidation or reduction to produce benzoyl or benzyl derivatives (based on benzoic acid, benzyl alcohol, respectively).

Following oral administration in rabbits, the majority of the chemical is excreted in the urine (~83 %) following oxidation to benzoic acid, which is excreted predominantly as hippuric acid (~68 % of the total dose). The other identified urinary metabolites were benzoylglucuronic acid (10 %), benzyl glucuronide (3 %), free benzoic acid (1.5 %) and trace amounts of benzyl mercapturic acid (<0.01 %) (NTP, 1990; US EPA, 2001; HSDB; REACH).

Following inhalation exposure, the chemical is absorbed almost completely and only 1.2 % of the administered dose was present in the respiratory tract 1.5 minutes after exposure. A biological half-life of 8.1 minutes in the blood was reported and elimination (via the renal system) was rapid and linear over time (HSDB; REACH).

The chemical also exists as a metabolite of toluene, and it has been determined to be the metabolite responsible for the production of reactive oxygen species (ROS) within the central nervous system (CNS) following toluene exposure. The chemical was found to exhibit specific effects by deactivating the antioxidant enzyme glutathione peroxidase, the main enzyme for removing hydrogen peroxide and organic hydroperoxides in the brain, and thus, causing neurotoxicity (HSDB) (see **Other Health Effects: Neurotoxicity**).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available animal and human data (see **Acute toxicity: observation in humans**) support this classification.

In an acute oral toxicity study conducted similar to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, groups of male Wistar rats were administered (by gavage) the chemical at doses of 0.8, 1.0, 1.1, 1.2, 1.3, 1.5, and 1.8 mL/kg bw and observed twice daily for 14 days. The acute median lethal dose (LD50) was reported to be 1.43 mL/kg bw (1430 mg/kg bw), with a mortality rate of 100 % (10/10) at the highest tested dose. Observed sub-lethal effects included sedation, staggering, weight loss and a rough coat (REACH).

In another acute oral toxicity study with limited data, male and female rats were administered the chemical at doses of 1100–1540 mg/kg bw. An LD50 of 1300 mg/kg bw was established (OECD, 2002; REACH).

Dermal

Although limited information is available, the chemical is likely to have low acute dermal toxicity in animal tests following dermal exposure.

In an acute dermal toxicity study in rabbits with limited available data, an LD50 of >1250 mg/kg bw was reported (OECD, 2002; HSDB; REACH).

Inhalation

Although limited data are available, the available information indicates that the chemical has moderate acute toxicity in animal tests following inhalation exposure and is recommended for classification (refer to **Recommendation** section).

In an acute inhalation toxicity study conducted according to OECD TG 436, Wistar rats (male/female) were exposed (nose only) to the vapours of the chemical at 1 and 5 mg/L for four hours and observed up to 14 days. Clinical effects were observed in most animals following exposure at 5 mg/L including lethargy, flat/hunched postures, ventrolateral recumbency, respiratory difficulties and piloerection. Four animals out of six (one male and three females) died following exposure at 5 mg/L. A median lethal concentration (LC50) of <5mg/L was established, based on mortalities at the highest tested dose (REACH).

An increased incidence of respiratory symptoms was noted among workers exposed to vapour of the chemical at atmospheric concentrations of >5 mg/m^3 (see **Acute toxicity: observation in humans**) (OECD, 2002).

Observation in humans

Case studies with limited documentation are available. The chemical has been reported to possibly cause respiratory failure, depression of the CNS and convulsions at high concentrations (HSDB).

A young woman died after ingesting 50–60 ml (700–2000 mg/kg) of the chemical. At autopsy, yellowish-white pulp with a strong odour of bitter almond was found in the stomach. The time between consumption and death was not specified. In another case, a man had to be revived from near death following ingestion of 40 ml of a derivative of the chemical (o-hydroxybenzaldehyde). Based on these two studies, a lethal oral dose of 600–900 mg/kg bw was calculated for the chemical in the absence of prompt treatment (NTP, 1990; EC, 2000; CIR, 2006).

In a case study, workers exposed to vapour of the chemical at atmospheric concentrations of >5 mg/m^3 reported an increased incidence of respiratory symptoms (OECD, 2002).

Corrosion / Irritation

Skin Irritation

Although limited data are available, the available information indicates that the chemical is not likely to be a skin irritant.

In two skin irritation studies (non-guideline) with limited data, the undiluted chemical (500 mg) was applied to the intact or abraded skin of New Zealand White rabbits for 24 hours with observation up to seven days. Although the exact details were not provided, slight skin irritation was observed (EC, 2000).

Eye Irritation

Although limited data are available, the chemical had been reported to be an eye irritant in animal studies. The available information is not sufficient to support a classification.

In an eye irritation study (non-guideline), one drop of the undiluted chemical was applied to the conjunctival sac of a rabbit. Observations were made at one, 24 and 48 hours following application. Immediate irritation effects were noted at one hour and within 24 hours, the anterior portion of the cornea was damaged. The cornea was cleared within 48 hours and only erythema of the conjunctiva and nictitating membrane was noted at this stage. Although the rabbit died on the sixth day, the death was not related to the application of the chemical (CIR, 2006; REACH).

In another eye irritation study (non-guideline) with limited data, the chemical (100 µL, concentration not stated) was instilled into the eyes of two rabbits and observed for seven days. The chemical was observed to be slightly irritating to the eyes (REACH).

Observation in humans

Case studies with limited documentation have been reported.

In an inhalation toxicity study, human volunteers were exposed to 4.5 ppm (19.5 mg/m^3) of the chemical for one minute. Irritation of the eyes and upper respiratory tract were observed. In an occupational study, workers exposed to the chemical vapour at atmospheric concentrations of >5 mg/m^3 reported symptoms of slight eye irritation and considerable skin irritation (OECD, 2002).

Sensitisation

Skin Sensitisation

Although the chemical has produced skin sensitisation reactions in some tests, based on the weight of evidence, the chemical is not likely to be a skin sensitiser. It is also noted that the chemical is rapidly metabolised to benzoic acid in the skin. Clinical reports of allergy to the chemical are rare and benzoic acid has also been reported not to produce sensitisation in clinical trials in humans (CIR, 2006).

In a Magnusson-Kligman skin sensitisation test conducted by the US EPA, guinea pigs (10/group) were initially exposed to the chemical intradermally by a 0.1 mL injection of 3 % chemical in paraffin oil followed by topical application to a patch of skin (occluded for 48 hours) of 15 % chemical in petrolatum. The skin was later challenged by a topical application (occluded for 24 hours) of 7 % chemical in petrolatum on a patch of skin. As the chemical failed to induce erythema in either group, the chemical was concluded not to be a skin sensitiser (CIR, 2006).

In a skin sensitisation study that compared four testing methods of 32 fragrance materials on Himalayan guinea pigs, the chemical tested positive for allergenicity in the Draize test (DT), the maximisation test (MT) and Freund's complete adjuvant (FCA) test. The guinea pigs were injected intradermally with the chemical at doses of 0.05 mL (0.1 % solution), 0.1 mL (5 % solution) and 0.05 mL (undiluted) for DT, MT and FCA, respectively (EC, 2000; CIR, 2006; REACH).

The chemical was reported to be non-sensitising in the open epicutaneous test (OET) for the same study as reported above. The guinea pigs were exposed to the chemical (undiluted, 0.03 , 0.1, 0.3, 1, 3, 10, or 30 %) at a dose of 0.1 mL on an 8 cm^2 area of shaved skin on the flank. Applications were repeated once a day for 21 days and the sites were scored for signs of irritation 24 hours following each treatment. The acute minimum irritating concentration was 10 % and after 21 exposures was 3 %. The animals were challenged with 3 % (minimum irritating concentration for day 21) or an unspecified lower concentration on a 2 cm^2 area of shaved skin at two weeks post-exposure. The sites were scored at 24, 48 and 72 hours. No sensitisation effects were observed (CIR, 2006; REACH).

In a guinea pig skin maximisation test (OECD TG 406), animals were injected intradermally with 2.7 % of the chemical and followed by three epidermal challenges with 2.1, 2.1 and 0.64 % of the chemical. It was noted that only one intradermal induction was performed and no additional topical induction. Also, there were three challenge reactions instead of one. The time between induction and challenge applications was also not stated. No sensitisation effects were observed (REACH).

Observation in humans

In a human study, maximisation test results on 25 volunteers treated at a concentration of 4 % of the chemical in petrolatum indicated no sensitisation effects. Patch test results reported positive reactions in 10/100 patients at a concentration of 5 % of the chemical in petrolatum. These positive outcomes occurred in patients with sensitivity to benzoic acid or vanillin (NTP, 1990; EC, 2000; OECD, 2002; HSDB; REACH).

Repeated Dose Toxicity

Oral

Based on the data available, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a repeated dose oral toxicity study, Fischer rats (male/female, 10/sex/dose) were administered the chemical by oral gavage at doses of 0, 50, 100, 200, 400 or 800 mg/kg bw/day, five days a week, for 13 weeks. Mortalities and histopathological changes including lesions in the brain (degeneration and necrosis of the cerebellum and necrosis in the hippocampus), renal tubular necrosis, hyperplasia and/or hyperkeratosis of the forestomach, and degeneration of the liver were observed in both sexes at the highest tested dose level. Depressed body weights (26 % lower than controls) were also observed for male rats at this dose. A no observed adverse effect level (NOAEL) of 400 mg/kg bw/day was established (NTP, 1990; OECD, 2002; CIR, 2006; REACH).

A similar repeated dose oral toxicity study on B6C3F1 mice (male/female, 10/sex/dose) was also conducted. The mice were administered the chemical by oral gavage at doses of 0, 75, 150, 300, 600 or 1200 mg/kg bw/day, five days a week, for 13 weeks. Within the first week of dosing, 9/10 males and 1/10 females died at the highest tested dose. Mild to moderate renal tubular degeneration in all males was observed in the high dose group and 1/10 males in the 600 mg/kg/day group. Depressed body weights (9 % lower than controls) were also observed for the males at 600 mg/kg bw/day. The NOAEL was determined to be 300 mg/kg bw/day for male mice and 600 mg/kg bw/day for female mice (NTP, 1990; OECD, 2002; CIR, 2006; REACH).

In another repeated dose oral toxicity study, similar to OECD TG 408, groups of Osborne–Mendel rats (male/female, five/sex/dose) were fed a powdered diet containing the chemical at concentrations of 1000 ppm for 28 weeks, or 10000 ppm (approximately 500 mg/kg bw/day) daily for 16 weeks. No effects on body weight or haematological parameters and no macroscopic/microscopic changes in selected organs were noted at 10000 ppm (CIR, 2006; REACH).

Dermal

No data are available.

Inhalation

Based on the limited data available, the chemical is not considered to cause serious damage to health from repeated exposure through inhalation.

In a repeated dose inhalation toxicity study conducted similarly to OECD TG 412, groups of Sprague Dawley (SD) rats (male/female, 14/sex/dose) were exposed (whole body) to the vapours of the chemical at 0, 500, 750 and 1000 ppm, six hours a day for 14 days. Significant reduction in body weight was observed for all males but only at 1000 ppm for females. Mortalities occurred in the two higher dose groups. All groups exhibited clinical toxicity symptoms including reduced motor activity, hypothermia, respiratory problems and nasal and ocular irritation. With increased concentrations, the severity of nasal and ocular irritation increased. At the two highest doses, the rats displayed aggressive behaviour and central nervous system symptoms (tremors, piloerection, diuresis, seizures and sensitivity to noise). The most prominent histopathological observation was goblet cell metaplasia in the respiratory epithelial lining of the nasal septum, which was found in males at doses 500 and 1000 ppm, but not in females. A no observed adverse effect concentration (NOAEC) could not be determined due to the clinical observations (indicative of neurotoxicity), hypothermia, and goblet cell metaplasia which were seen at concentrations of 500 ppm and above. The lowest observed adverse effect concentration (LOAEC) was reported to be 500 ppm in this study (CIR, 2006; HSDB; REACH).

In another repeated dose inhalation toxicity study with limited documentation (non-guideline), rats were exposed to the chemical at 186 ppm (803 mg/m^3), four hours a day, five days a week for two weeks. Respiratory irritation was observed during exposure. No other effects were reported (EC, 2000; OECD 2002).

Observation in humans

Limited data are available for repeated dose toxicity in humans. Available case studies indicated that repeated exposure to the chemical may not cause damage to health at low concentrations.

In a study with limited data reported, patients with ulcers and healthy volunteers (numbers unspecified) were exposed to daily doses of the chemical at 0.25–0.50 g in a test meal. Although no signs of toxicity were reported, reduced pepsin activity was diagnosed in the stomach. In another case study, around 102 cancer patients were treated (orally or rectally) with daily doses of 10 mg/kg bw beta-cyclodextrin benzaldehyde (0.83 mg/kg bw of the chemical) for a range of two weeks to two years. No treatment-related changes in haematology or clinical chemistry were reported (EC, 2000).

Increased incidences of respiratory problems were observed in workers exposed to atmospheric concentrations of the chemical not exceeding 5 mg/m^3 (OECD, 2002).

Genotoxicity

Overall, the data indicate that the chemical has no mutagenic or genotoxic potential.

Although there is no mutagenic activity in bacterial systems, the chemical does have weak clastogenic effects in some mammalian cell assays. There are also no in vivo data available.

The chemical gave negative results in several in vitro bacterial reverse mutation assays with *Salmonella typhimurium* at concentrations up to 3333 μg/plate. Induction of chromosomal aberrations was also not observed in Chinese hamster ovary (CHO) cells, treated with the chemical up to 500 μg/mL in the absence of S9 or with up to 1600 ug/mL with S9 (NTP, 1990; REACH).

In an in vitro chromosomal aberration assay (OECD TG 473) in the Chinese hamster cell line B241, a significant percentage (13 %; 21/162) of the cells displayed abnormalities following exposure to a concentration of 5.3 nM of the chemical for 24 hours (CIR, 2006). Cytogenetic tests with CHO cells reported an increased number of sister chromatid exchanges at doses of 50 μg/ml and 160 μg/ml in the absence of S9 or at 1600 μg/mL with S9 (NTP, 1990; HSDB; REACH).

The chemical gave positive results in a mouse lymphoma forward mutation assay (OECD TG 476) with mouse lymphoma L5178Y cells. The concentrations of the chemical tested in this assay were 0, 50, 100, 200, 400, and 800 μg/mL. Although significant increases in mutant fractions were observed at a dose of 400 μg/mL, the positive response was noted to be close to the cytotoxic dose of 640 μg/ml (HSDB; REACH).

Negative results were obtained with the chemicals in an in vivo sex-linked recessive lethal test with *Drosophila melanogaster* (NTP, 1990; OECD, 2002; HSDB; REACH).

Carcinogenicity

Although the chemical has been reported to have 'some evidence of carcinogenic activity' in B6C3F1 mice, there was 'no evidence of carcinogenic activity' in Fischer 344 rats receiving 200 or 400 mg/kg bw/day (NTP, 1990). It was further concluded that the increased incidences of pancreatic acinar cell neoplasms in male rats and squamous cell papillomas of the forestomach in mice were probably due to the high concentrations of corn oil (mild irritant and mitogen) used as a vehicle in these studies (US EPA, 2001). The chemical is also considered not to have mutagenic or genotoxic potential (see **Genotoxicity**). Therefore, the chemical is not considered to have carcinogenic potential.

In a combined chronic toxicity–carcinogenicity study (OECD TG 451), groups of eight-week-old Fischer 344 rats (male/female, 50/sex/dose) were administered (gavage) the chemical in corn oil at doses of 200 or 400 mg/kg bw, five days a week for two years. At the highest dose, mortality in male rats was significantly higher than the controls. No dose-related effects on body weight and clinical signs were observed. As squamous cell papillomas of the forestomach were seen in only two female rats in the high dose group and there was a lack of supporting hyperplasia, these were not considered to be due to the administration of the chemical. Significant increases in the incidences of pancreatic acinar cell hyperplasia and tumours were observed in male rats only at the high dose. Unpublished National Toxicology Program (NTP) studies indicated that pancreatic acinar cell tumours

found in rats gavaged with corn oil were not autunomous as these tumours failed to transplant. Therefore, based on the facts that these tumours failed to transplant, were present in variable numbers in control animals, and increased only at the high dose, it was concluded that pancreatic acinar cell hyperplasia and tumours were not considered as evidence of carcinogenic activity for the chemical (NTP, 1990; EC, 2000; HSDB; REACH). It was further concluded that the increased incidence of tumours specific to male rats in this study was probably due to the use of corn oil as a vehicle in this study (US EPA, 2001).

In the same carcinogenicity study, groups of eight-week-old B6C3F1 mice (male and female, 50/sex/dose) were administered (gavage) the chemical in corn oil at doses of 200 or 400 mg/kg bw (in males), 300 or 600 mg/kg bw (in females), five days a week for two years. Although no significant differences in mean body weights and survival were observed between any groups of mice, effects were noted in the forestomach of mice. The incidences of uncommonly occurring squamous cell

papillomas of the forestomach in both exposure groups were significantly greater as compared to the controls (male: vehicle control, 1/50; low dose, 2/50; high dose, 5/50; female: 0/50; 5/50; 6/50). The increased incidences of papillomas were accompanied by significantly increased incidences of focal hyperplasia in the forestomach in both sexes of the 400 mg/kg bw group and in females of the 200 mg/kg bw group, compared with vehicle controls. The NTP considered that the increase in papillomas was due to a concurrent increase in hyperplasia following treatment with the chemical and concluded that there was 'some evidence of carcinogenicity' in mice. It was also concluded male and female mice might have been able to tolerate higher doses (NTP, 1990; REACH).

Reproductive and Developmental Toxicity

Although limited data are available, the available information indicates that the chemical does not show specific reproductive or developmental toxicity.

Benzyl derivatives, including benzaldehyde, have been reported to produce no evidence of reproductive and developmental toxicity during various studies. It was also stated that as benzyl derivatives generally follow similar metabolic pathways, studies conducted on benzyl derivatives provide adequate evidence for benzaldehyde (US EPA, 2001). As part of reviewing the reproductive toxicity and teratogenicity of benzaldehyde and related compounds (benzyl acetate, benzyl alcohol, and benzoic acid and its salts), the Joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) Expert Committee on Food Additives concluded that 'delayed development and reduced foetal and postnatal pup body weights were observed in developmental toxicity studies in rats, mice, hamsters and rabbits, but only at doses that were toxic to the mother' (CIR, 2006).

In a poorly-documented one-generation reproductive toxicity study (non-guideline), male and female rats were administered the chemical by oral gavage at doses of 0 or 5 mg/kg bw/day in oil, once every second day for 32 weeks. Dosing commenced at 75 days before breeding with untreated males; two pregnancies per rat were studied, one at 75 days and one at 180 days. The number of gestating females, number of live-born offspring, pup weights at birth and on postnatal days 7 and 21, and pup viability were recorded. The incidences of pregnancy were reported to be lower for treated females compared with controls. All other parameters were reported to be similar between the treatment and control groups. It was concluded that the treatment did not cause a significant change in any of the reproductive parameters measured. (US EPA, 2001; OECD, 2002; CIR, 2006; REACH).

Other Health Effects

Neurotoxicity

Although appropriately conducted neurotoxicity studies are not available, several animal studies using the chemical have indicated the possibility for some neurotoxic effects (See **Toxicokinetics**). The chemical has also been described as having narcotic effects on humans at high concentrations (NTP, 1990).

In a poorly-documented study on the sedative effects of fragrance compounds and essential oils, Swiss mice were exposed by inhalation to undiluted vapours of the chemical for one hour. A reduction in motility (~43 %), compared with the controls, was reported (CIR, 2006).

The chemical has been implicated in causing CNS disturbances in rats, as a result of ROS formation in synaptosomal fractions. The chemical rapidly and very efficiently inactivates the antioxidant enzyme glutathione peroxidase (GPX) but has no effect on other antioxidant enzymes tested. Other structurally related and unrelated aldehydes tested did not exhibit the same inactivating capacity. Removing this enzyme could expose the brain to sustained oxidative injury, thus contributing to CNS damage (Tabatabaie, 1996).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral and inhalation exposure).

Public Risk Characterisation

The general public might be exposed to the chemical through dermal and/or inhalation routes when using domestic products containing the chemical. Considering that the highest use concentration of the chemical in cosmetics has been reported to be 0.5 % in perfumes, the stated concentration is not considered to be sufficiently high to cause any significant human health concerns. 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 might 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 health effects, the chemical can pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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 the **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]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)

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

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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.

References

ChemIDPlus, CAS no 100-52-7, http://chem.sis.nlm.nih.gov/chemidplus. Accessed July 2014

Cosmetic Directive (CosIng). Benzaldehyde (202-860-4). Accessed July 2014 at http://ec.europa.eu/consumers/cosmetics/cosing/

Cosmetic Ingredient Review (CIR) 2006. Final Report on the Safety Assessment of Benzaldehyde. International Journal of Toxicology 25(11) pp. 11-27.

European Commission (EC) 2000. IUCLID Dataset on Benzaldehyde (CAS No. 100-52-7). Accessed July 2014 at http://esis.jrc.ec.europa.eu/doc/IUCLID/datasheet/100527.pdf

Galleria Chemica. Accessed July 2014 at https://jr.chemwatch.net/galleria/

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed July 2014 at http://toxnet.nlm.nih.gov.

National Toxicology Program (NTP) 1990. Toxicology and Carcinogenesis Studies of Benzaldehyde (CAS No. 100-52-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Accessed July 2014 at http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr378.pdf

OECD (2002). SIAR on Benzaldehyde (100-52-7). Accessed July 2014 at http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?key=c05dffb0-e5df-4831-bf0d-0a6942bc80e0&idx=0

Personal Care Product Council (INCI Dictionary). Accessed July 2014 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

REACH Dossier. Benzaldehyde (CAS No. 100-52-7). Accessed July 2014 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed July 2014 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Substances in Preparations in Nordic Countries (SPIN). Accessed July 2014 at http://195.215.202.233/DotNetNuke/default.aspx

Tabatabaie T& Floyd RA 1996. Inactivation of Glutathione Peroxidase by Benzaldehyde. Toxicology and Applied Pharmacology 141(2) pp. 389-393..

US Environmental Protection Agency (EPA), 2001. High Production Volume (HPV) Challenge program's Robust Summaries and Test Plans: Benzyl Derivatives. Accessed July 2014 at http://www.epa.gov/hpv/pubs/summaries/benzylde/c13450tc.htm

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