Benzoic acid, 2-hydroxy-, phenylmethyl ester: Human health tier II assessment

01 July 2016

CAS Number: 118-58-1

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.

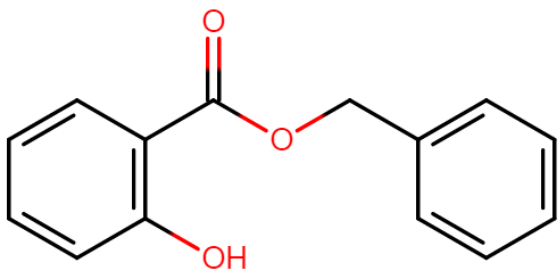
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	benzyl salicylate salicylic acid, benzyl ester benzyl 2-hydroxybenzoate phenylmethyl 2-hydroxybenzoate
Structural Formula	
Molecular Formula	C14H12O3
Molecular Weight (g/mol)	228.25
Appearance and Odour (where available)	Colourless liquid. herbal oily sweet
SMILES	C(=O)(c1c(O)cccc1)OCc1ccccc1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through 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 Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS) (Bailey, 2011); the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and various international assessments (Adams et al., 2005; EFSA, 2008; Singhal et al., 2011; the International Fragrance Association (IFRA) standard (IFRA, 2009)).

The chemical has reported cosmetic uses, including:

- in perfumes and fragrances;
- in personal care products; and
- as an ultraviolet (UV) radiation absorber in cosmetic products with UV protection function.

The chemical has reported domestic uses, including in:

- polishes and waxes;
- softeners;
- surface treatments.
- air care products; and
- washing and cleaning products.

The chemical has reported non-industrial uses, including:

- in pharmaceuticals;
- as a flavouring agent; and
- in biocides.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed in the EU Cosmetic Regulation EC No. 1223/2009, Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down (Galleria Chemica). It states that 'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article19(1)g when its concentration exceeds:

- 0.001% in leave-on products

- 0.01% in rinse-off products.'

Additionally, IFRA has restricted use of the chemical in finished products to 15.79 % (IFRA, 2009).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are identified.

Health Hazard Information

The chemical is an ester of benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7). Metabolism of an ester results in the initial formation of the parent alcohol and acid, which may be further metabolised. The toxicological properties of these chemicals (NICNASa, NICNASb) are therefore relevant to the systemic toxicity of benzyl salicylate.

Toxicokinetics

In an in vitro dermal penetration study conducted using human abdominal skin, 0.2 mL of the chemical was percutaneously administered for 72 h. It was reported that 0.031 % of the chemical traversed the skin (Belsito et al., 2007).

In an in vitro skin absorption study, the chemical in ethanol was applied to excised naked rat skin at 1, 3, or 10 % for 24 h. Test substance migration into receptor fluid was measured to be 62.7, 58.8 and 40.3 % for the 1, 3 and 10 % concentrations, respectively. When the same test was conducted using guinea pig skin for 16 h, 3.5 %, 1.7 % and 0.9 % of the solution migrated through the skin into the receptor fluid for the 1, 3 and 10 % concentrations, respectively (Belsito et al., 2007).

Acute Toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

The median oral lethal dose (LD50) in male rats was determined to be 2227 mg/kg bw (Belsito et al., 2007; Lapczynski et al., 2007; US EPA, 2010; REACH).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

The median dermal LD50 in albino rabbits was determined to be 14 150 mg/kg bw. Observed sub-lethal effects included behavioural depression, slow respiration and a loss of the righting reflex (Belsito et al., 2007; Lapczynski et al., 2007; REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in animal studies and in humans (see ***Observation in humans*** below). The effects are not sufficient to warrant hazard classification.

In a study conducted according to OECD TG 404, female New Zealand White (NZW) rabbits (n = 4) were semi-occlusively administered 0.5 mL of the neat chemical on shaved flanks for 4 h and the animals were observed for seven days. The mean oedema and erythema scores were 0.2/4 and 0.6/4, respectively (Belsito et al., 2007; REACH).

In a study conducted in female NZW rabbits (n = 3), the chemical (0.5 mL) was semi-occlusively applied to the shaved flanks for 4 h and animals observed after 1, 24, 48 and 72 h and 7 days after removal of the patch. After 1 h, well defined erythema and slight oedema were observed in two rabbits and very slight oedema in the third rabbit. All effects were reversed by 72 h (REACH).

As part of a phototoxicity study conducted in female Dunkin Hartley guinea pigs (n = 5), the chemical was dermally administered (non-occlusively) at concentrations of 5, 10 or 30 % in acetone for 24 or 48 h. No irritation was observed at 5%; slight erythema was observed at 10 % in 1/5 animals and in all animals at 30 % (Belsito et al., 2007).

Eye Irritation

The available studies tested the chemical at a 10 % concentration only. Considering the effects observed at this concentration, the chemical is expected to be at least irritating to the eyes if exposed at higher or neat concentrations, warranting hazard classification (see **Recommendation** section).

In an in vivo study (Draize method) conducted in albino rabbits (n = 3), 0.1 mL of the chemical at a 10 % concentration in alcohol was instilled into the right eye and animals observed for 10 days. Mild conjunctival irritation was observed in all rabbits and corneal opacity in one rabbit. All effects were reversed within seven days. The mean scores reported for iritis (0/4), conjunctival redness (1.89/4), chemosis (1.22/4) and corneal opacity (0.33/4) were below the cut-off for classification. However, individual average (24, 48 and 72 h) scores for two rabbits for conjunctival redness were 2/4, which is sufficient for classification by GHS criteria (but not by Approved Criteria). The chemical was determined to be irritating (Lapczynski et al., 2007; REACH).

In an ex vivo study conducted according to OECD TG 437, 0.75 mL undiluted chemical was applied to isolated bovine corneas for 10 minutes, followed by rinsing and a further 120 minute incubation. An irritancy score of 0/5 was reported and it was concluded that the chemical is not an ocular corrosive or severe irritant (REACH).

Observation in humans

In several skin irritation studies in humans, the chemical at 15–100 % was applied to the skin via an occluded patch for 4–48 h (Belsito et al., 2007; Lapczynski et al., 2007; REACH). One study reported irritation in 2/22 subjects exposed to the chemical at 30 % (Belsito et al., 2007).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser, warranting hazard classification (see **Recommendation** section).

In a murine local lymph node assay (LLNA), female CBA/JN mice (n = 4/dose) were administered 25 µL of the chemical topically at 10 % in 4:1 acetone/olive oil vehicle to the left and right ear lobe for three days. After three days, the mice were injected with 20 µCi ^{3}H-thymidine (in 250 µL phosphate-buffered solution (PBS)) into their tail vein. Five hours later, the animals were euthanised and auricular (ear) lymph nodes were analysed. The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was determined to be 1.5 % (375 µg/cm^2) and the chemical was categorised as a weak sensitiser (Belsito et al., 2007; Lapczynski et al., 2007; RIVM, 2008).

In an LLNA conducted according to OECD TG 429, female CBA/Ca mice (n = 4/dose) were treated with 25 µL of the chemical at 2.5, 5, 10, 25 or 50 % w/v in 1:3 ethanol:diethyl phthalate vehicle. The EC3 value was determined to be 2.9 % (725 µg/cm^2) and it was concluded that the chemical was sensitising (Belsito et al., 2007; Lapczynski et al., 2007; SCCP, 2012; REACH).

In a guinea pig maximisation test (GPMT), female Hartley guinea pigs (n = 20/dose) were intradermally induced at 10 % in liquid paraffin and topically induced with the chemical at 50 % in white petrolatum, followed by a challenge using 5, 10 or 20 % of the chemical in white petrolatum. Positive reactions were observed at the 20 % challenge (2/20) and there were some 'questionable' reactions at other concentrations (3/20 at 5 %, 5/20 at 10 % and 4/20 at 20 %) (Belsito et al., 2007; Lapczynski et al., 2007).

In another GPMT conducted in female Hartley albino guinea pigs (n = 10/dose), the chemical was applied by intradermal induction at 10 % in liquid paraffin and by topical induction at 30 % in ethanol. Animals were then topically challenged with the chemical twice, three weeks apart, at 0.003, 0.01 or 0.03 % in ethanol and observed at 24, 48 and 72 h. No reactions were observed after the first challenge. After the second challenge, positive reactions were reported at 0.03 % after 24 h, and at all concentrations after 48 and 72 h (Belsito et al., 2007; Lapczynski et al., 2007).

In a GMPT in female albino Dunkin Hartley guinea pigs (n=8/dose), animals were intradermally induced with the chemical at 10 %. Following a seven day rest period, the chemical at 10 % in acetone was topically applied to the shoulder region for 48 h. Two weeks later, challenge doses of the chemical at 5, 10 or 20 % in acetone were applied to the shaved flanks of each animal and observations made at 24, 48 and 72 h. Positive reactions were observed at all concentrations (Belsito et al., 2007; Lapczynski et al., 2007).

In two other GPMTs conducted using outbred Himalayan white-spotted guinea pigs (males and females, number not specified) or Hartley guinea pigs (n = 10, sex not specified), sensitisation was not reported. In the former study, the chemical was used at 5 % for intradermal induction, 25 % in petrolatum for topical induction and <0.1 % in petrolatum for the topical challenge; the challenge concentration was reported to be a 'sub-irritant' concentration. In the latter study, the chemical was applied at 1 % in ethanol for intradermal induction and at 100 % for the challenge; no further study details are available (Lapczynski et al., 2007).

Observation in humans

In human patch test studies, results for sensitisation were varied.

The IFRA reported a No Expected Sensitisation Induction Level (NESIL) of 17 700 µg/cm^2 based on a human maximisation test and therefore classified the chemical as a weak sensitiser (IFRA, 2009).

In five maximisation tests using human volunteers (n = 22–25/study, males and females), the chemical was administered at 20–30 % in petrolatum. Reactions were observed in two studies, affecting 2/25 and 1/25 subjects at 20 %. No positive reactions were reported at 30 % (Belsito et al., 2007; Lapczynski et al., 2007).

In a study that was conducted to determine the optimal patch testing concentration of the chemical, humans (n = 212) were dermally exposed to the chemical at 5 % in petrolatum. Positive reactions were reported in 12/212 subjects (Lapczynski et al.,

2007).

In three human repeated insult patch tests (HRIPT) conducted on volunteers (n = 35, 52 or 101; males and females), the chemical was administered at 5–15 % in various vehicles (diethyl phthalate:ethanol (3:1) or dimethyl phthalate or alcohol SD39) and observations were made up to 144 h after the final challenge exposure. Positive reactions were not observed in any study (Belsito et al., 2007; Lapczynski et al., 2007).

In a human patch test (HPT), 30 volunteers were dermally exposed to 0.2 mL of the chemical via application to the skin of the upper outer arm for 4 h and observed for 72 h. No reactions were reported (Basketter et al., 2012).

Repeated Dose Toxicity

Oral

No data are available for the chemical. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), the chemical is not expected to cause serious health effects from repeated oral exposure, except at high doses.

Two studies were conducted using benzyl alcohol. In the first study, Fischer 344 (F344) rats (n = 8–10/sex/dose) were administered the chemical via gavage at doses 0, 50, 100, 200, 400 or 800 mg/kg bw/day, once a day, five days per week for 13 weeks. The no observed adverse effect level (NOAEL) was determined to be 400 mg/kg bw/day based on signs of neurotoxicity, including necrosis of the hippocampus in 9/9 females and 7/7 males, at the highest dose. Skeletal muscle necrosis was observed in 5/10 males and, haemorrage and atrophy in 8/20 males at 800 mg/kg bw. In the second study, F344 rats (n = 5/sex/dose) were administered the chemical by gavage at doses of 0, 125, 500, 1000 and 2000 mg/kg bw/day, five days per week for 16 days. The NOAEL was determined at 500 mg/kg bw/day based on observation of blood around the nose and mouth, subcutaneous haemorrhage, lethargy, blood in the urine and death, observed at the two highest doses. Mortalities were reported in the 1000 mg/kg bw dose in males (2/5) and females (3/5) (REACH).

In a subacute toxicity study conducted using salicylic acid, male albino rats (n = 10/dose) were administered the chemical in diet at 9.35, 69.4 or 237.2 mg/kg bw/day for 28 days. The NOEL was detemined to be 237.2 mg/kg bw/day as adverse health effects were not reported at any of the doses (REACH).

Dermal

No data are available.

Inhalation

No data are available for the chemical. However, based on data for the metabolite benzyl alcohol (CAS No. 100-51-6), the chemical is not expected to cause serious health effects from repeated inhalation exposure.

In a subacute toxicity study (according to OECD TG 412) conducted using benzyl alcohol, SD rats (n = 10/sex/dose) were exposed (nose only) to the chemical as an aerosol at analytical concentrations of 41, 102, 290 or 1072 mg/m^3 for 6 h/day, five days per week, for four weeks. Due to the votatility of the chemical, the particle size could only be calculated for the highest dose (3.3 µm). No adverse effects were reported; thus, the no observed adverse effect concentration (NOAEC) was determined at 1072 mg/m^3 (REACH).

Genotoxicity

Based on the weight of evidence of the limited available data on the chemical, and data for the metabolite benzyl alcohol (CAS No. 100-51-6), the chemical is not considered to be genotoxic.

Negative results were reported for one in vitro point mutation assay (Ames test) using the parent chemical, where *Salmonella typhimurium* strains TA98, 100, 1535 and 1537 were exposed at 0.3–666 µg/plate, with or without metabolic activation (US EPA, 2010; REACH; TOXNET).

No in vivo data are available for the parent chemical.

In vitro tests using the metabolite benzyl alcohol gave positive results for clastogenicity (OECD, 2001):

- negative results in an Ames test conducted using *S. typhimurium* strains TA98, 100, 1535 and 1537 exposed to benzyl alcohol at concentrations up to 666 µg/mL, with and without metabolic activation;
- negative results without metabolic activation but positive results with metabolic activation in a cytogenic assay conducted using Chinese hamster ovary (CHO) cells exposed to benzyl alcohol at concentrations up to 5000 µg/mL;
- positive results at concentrations ≥3000 µg/mL with and without metabolic activation, in a mouse lymphoma assay using L5178Y cells exposed to benzyl alcohol at concentrations up to 5000 µg/mL;
- positive results at 17.9 mM only in a transformation assay conducted using BALB/c3T3 cells exposed to benzyl alcohol at concentrations 5–20 mM without metabolic activation; and
- positive results in a sister chromatid exchange (SCE) assay conducted using CHO cells exposed to benzyl alcohol at 16-5000 µg/mL with and without metabolic activation.

However, in vivo tests using the metabolite benzyl alcohol gave negative results (OECD, 2001):

- negative in a micronucleus assay conducted using ddY mice (number and sex not specified) exposed to benzyl alcohol for 24 h at doses 0, 50, 100 or 200 mg/kg bw/day via intraperitonal (I.P.) injection; and
- negative in a replicative DNA synthesis test in rat hepatocytes from F344 rats (number and sex not specified) administered a single dose of benzyl alcohol via gavage at 0, 300 or 600 mg/kg bw/day.

Carcinogenicity

No data are available for the chemical. However, based on the data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), the chemical is not considered to be carcinogenic.

Groups of B6C3F1 mice (n = 50/sex/dose) and F344/N rats (n = 50/sex/dose) were administered benzyl alcohol in corn oil at doses of 0, 100 or 200 mg/kg bw/day and 0, 200 or 400 mg/kg bw/day, respectively, for five days per week for 103 weeks. Negative trends were noted in the incidences of anterior pituitary gland neoplasms in female rats (control 29/50; low dose 17/47; high dose 9/49) and Harderian gland adenomas in male mice (8/50; 3/50; 2/50). It was concluded that the chemical showed no evidence of carcinogenic activity (NICNASa).

In a study conducted on Saitama rats (male and female; number not specified), salicylic acid was administered in diet at 0.5 %, and increased to 1 % after eight months. Animals were observed for 230-331 days. No tumours developed, the stomach showed fibrosis and an ulcer in one rat. The liver showed cloudy hypertrophy and the spleen showed fibrosis, haemosiderosis and atrophy. The chemical was determined to be non-carcinogenic (REACH).

Reproductive and Developmental Toxicity

No data are available for the chemical. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS 69-72-7), the chemical is not considered to cause developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

In two developmental toxicity studies, both conducted in pregnant CD-1 mice (n = 50/dose), benzyl alcohol was administered via gavage at doses of 550 or 750 mg/kg bw/day on gestation days 6–15 or 7–14 respectively. Clinical signs of maternal toxicity were observed at 750 mg/kg bw/day and included hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnoea, swollen or cyanotic abdomen, and piloerection. On day 18, maternal body weight was significantly decreased. Significant reductions in pup body weight were reported on days one and three post-partum, including a lower mean pup weight

per litter, mean litter weight change between day one and day three post-partum, and mean pup weight change between days one and three post-partum. No differences in pup survival were observed by day three post-partum. The NOAEL and LOAEL were determined in separate studies as <550 mg/kg bw/day and 750 mg/kg bw/day, respectively (NICNASa)

In a developmental toxicity study conducted in female SD rats (number not specified), salicylic acid was administered by gavage at a single dose of 0, 120, 180, 240 or 300 mg/kg bw on gestation day nine. Animals were sacrificed on day 20 of pregnancy. At the three highest doses, bodyweight loss was observed in the dams due to decreased food consumption. There was also an increase incidence of the 27th (presacral) vertebrae in the foetuses. The NOAEL for maternal and foetal toxicity was determined at 120 mg/kg bw (REACH).

Other Health Effects

Endocrine Disruption

The oestrogenic activity of the chemical has been assessed in vitro, using MCF7 human breast cancer cells. The chemical was used in a competitive binding assay to the cytosolic oestrogen receptor (ER) of MCF7 cells; a competitive binding assay to human recombinant ERa and ERβ; a gene expression assay using the stably transfected ERE-CAT reporter gene in MCF7 cells; and a cell proliferation assay. The chemical mimicked oestrogenic responses in all assays. In the competitive binding assays, 3H-oestradiol was partially displaced by the chemical (when used at 3×10^6 molar excess) from cytosolic ER of MCF7 cells and from human recombinant ERa and ERβ. In the gene expression assay, the chemical increased the expression of the oestrogen-responsive reporter gene (ERE-CAT) and the endogenous oestrogen-responsive pS2 gene when cells were exposed at concentrations of 0.05–0.5 mM. In the cell proliferation assay, the chemical increased proliferation of oestrogen-dependent cells over a seven day period; proliferation was inhibited by an anti-oestrogen drug (fulvestrant). However, it was reported that the chemical was less potent (requiring 1 mM versus 0.1 μM) and took 2.5-fold longer duration (35 days versus 14 days) to achieve a similar magnitude of proliferation as endogenous 17β-oestradiol (CIR, 2011).

Further conclusions on the endocrine disruption potential of the chemical cannot be made. This is an area of concern given the lack of data available for reproductive and developmental toxicity, and due to structural similarity of the chemical to monobenzyl phthalate (CAS No. 2528-16-7) which is known to have anti-androgenic activity and the potential to impair fertility and cause teratogenic effects (NICNAS, 2015).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

The chemical can also cause eye irritation.

Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemical is reported to be used in cosmetic/domestic products overseas at concentrations up to 7 % (IFRA, 2007).

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products. In the absence of any regulatory controls, the characterised critical local health effects have the potential to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

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

Given the critical local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure 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 the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in domestic and cosmetic products. Due to the toxicity profile at the concentrations reported to be potentially in use, this chemical should be considered for listing the Poisons Standard — *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) for labelling as a skin sensitiser, consistent with the *Scheduling Policy Framework* guidelines. Exemptions to scheduling might be applicable at low concentrations.

Consideration should be given to the following:

- the known uses of the chemical—although there is no information to confirm that the chemical is currently used in cosmetic and domestic products in Australia, it is reported to be used in cosmetic and domestic products overseas at concentrations up to 7 % (IFRA, 2007);
- there are overseas restrictions for the use of the chemical in cosmetics;
- the chemical is recommended for classification as an eye irritant and a skin sensitiser; and
- there are limited data on genotoxicity and no data on reproductive and developmental toxicity.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal or 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:

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

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

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

Obligations under workplace health and safety legislation

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

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and

- managing risks arising from storing, handling and using a hazardous chemical.

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

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

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

References

Adams TB, Cohen SM, Doull J, Feron VJ, Goodman JI, Marnett LJ, Munro IC, Portoghese PS, Smith RL, Waddell WJ, Wagner BM 2005. The FEMA GRAS assessment of hydroxy- and alkoxy-substituted benzyl derivatives used as flavor ingredients. Food and Chemical Toxicology 43 pp. 1241–1271.

Annex I to the International Fragrance Association (IFRA) standard 2007. Accessed March 2016 at: www.ifraorg.org/view_document.aspx?docId=23602

Approved criteria for classifying hazardous substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.nohsc.gov.au/pdf/Standards/approved_criteriaNOHSC1008_2004.pdf

Bailey, JE (ed.) 2011. Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition, Personal Care Products Council, Washington, D.C.

Basketter D, Jirova D, Kandarova H 2012. Review of skin irritation/corrosion Hazards on the basis of human data: A regulatory perspective. Interdiscip. Toxicology, 5(2) pp. 98–104.

Belsito D, Bickers D, Bruze M, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG, Tagami H 2007. A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients. Food and Chemical Toxicology, 47 pp. S318–S361.

Cosmetic Ingredient Review (CIR) 2011. Amended Final Report on the Safety Assessmentof Benzyl Alcohol, and Benzoic Acid and its Salts and Benzyl Ester. Accessed at http://www.alegesanatos.ro/dbimg/files/Benzyl%20Alcohol%20-%20Benzoic%20Acid.pdf

Ema M, Miyawake E, Hirose A, Kamata E 2003. Decreased anogenital distance and increased incidence of undescended testes in fetuses of rats given monobenzyl phthalate, a major metabolite of butyl benzyl phthalate. Reproductive toxicology, 17(4) pp. 407-412. Accessed at http://www.ncbi.nlm.nih.gov/pubmed/12849851

European Commission Cosmetic Ingredients and Substances (CosIng) database. Accessed Month 2016 at http://ec.europa.eu/consumers/cosmetics/cosing/

European Food Safety Authority (EFSA) Journal 2008. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission. Accessed March 2016 at http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/afc_op_ej637_FGE52_op_en%2C3.pdf

Galleria Chemica. Accessed March 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

International Fragrance Association (IFRA) standard – Benzyl salicylate, 42nd amendment, 2009. Accessed March 2016 at www.ifraorg.org/view_document.aspx?docId=23153

Lapczynski A, McGinty D, Jones L, Bhatia S, Letizia CS, Api AM 2007. Fragrance material review on benzyl salicate. Food and Chemical Toxicology, 45 pp. S362–S380.

National Industrial Chemicals Notifcation and Assessment Scheme (NICNAS). Human Health Tier II Assessment for benzenemethanol (CAS 100-51-6). Accessed May 2016 at https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1784#cas-A_100-51-6

National Industrial Chemicals Notifcation and Assessment Scheme (NICNAS). Human Health Tier II Assessment for salicylic acid (CAS 69-72-7). Accessed May 2016 at https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=138#cas-A_69-72-7

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2015. Priority Existing Chemical (PEC) assessment report no. 40: Butyl benzyl phthalate (BBP). Accessed May 2016 at https://www.nicnas.gov.au/__data/assets/word_doc/0006/16737/BBP-PEC-report-7-July-2015.docx

National Institute for Public Health and the Environment (RIVM) 2008. Allergens in consumer products. Report 320025001/2008. http://www.chemiezone.nl/chemiezone/images/rapport%20rivm_tcm708-444676.pdf

Ozakia H, Sugihara K, Tamura Y, Fujino C, Watanabe Y, Uramaru N, Sone T, Ohta S, Kitamura S 2015. Hydrolytic metabolism of phenyl and benzyl salicylates, fragrances and flavoring agents in foods, by microsomes of rat and human tissues. Food and Chemical Toxicology, 86 pp. 116–123.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 100-51-6. Accessed May 2016 at http://echa.europa.eu/registration-dossier/-/registered-dossier/14748/7/6/2/?documentUUID=db945fe8-7cfb-4445-af17-bdd7c00cd33b

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 118-58-1. Accessed March 2016 at http://echa.europa.eu/registration-dossier/-/registered-dossier/16100/7/3/2/?documentUUID=2929bd9b-b7c1-44dd-a5af-8452d788230a

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 69-72-7. Accessed May 2016 at http://echa.europa.eu/registration-dossier/-/registered-dossier/14544

Safe Work Australia. Hazardous Substances Information System (HSIS). Accessed March 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Scientific Committee on Consumer Products (SCCP) 2012. Opinion on Fragrance allergens in cosmetic products. Accessed March 2016 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf

Singhal M, Khanna S, Nasa A (2011). Cosmeceuticals for the skin: An overview. Asian Journal of Pharmaceutical and Clinical Research, 4(2) pp. 1–6.

Substances in Preparations in Nordic Countries (SPIN). Accessed March 2016 at http://195.215.202.233/DotNetNuke/default.aspx

The Good Scent Company data on benzyl salicylate (CAS No. 118-58-1). Accessed March 2016 at http://www.thegoodscentscompany.com/data/rw1001792.html

The Organisation for Economic Cooperation and Development (OECD) High Production Volume (HPV) chemical program. Accessed March 2016 at http://www.oecd.org/chemicalsafety/risk-assessment/33883530.pdf.

The Organisation for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) 2001. SIDS Initial Assessment Report: Benzoates. Accessed May 2016 at www.inchem.org/documents/sids/sids/BENZOATES.pdf

The United States (US) Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR). CAS no. 118-58-1. Accessed March 2016.

Toxicology Data Network (TOXNET). Benzyl Salicylate (CAS no. 118-58-1). Accessed March 2016 at http://toxnet.nlm.nih.gov/.

United States (US) Environmental Protection Agency (EPA) 2010. Screening-level hazard characterisation: Benzyl Derivatives Category. Accessed May 2016 at http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.188.3737&rep=rep1&type=pdf

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed March 2016 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

Last update 01 July 2016

Share this page