Benzoic acid: Human health tier II assessment

28 June 2013

CAS Number: 65-85-0

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.

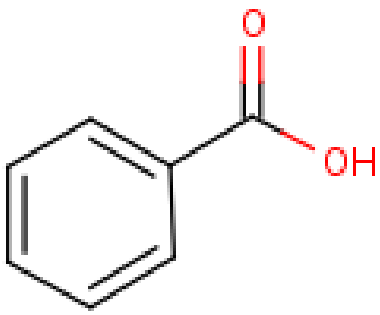
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Benzenecarboxylic acid Benzeneformic acid Phenylcarboxylic acid Benzenemethanoic acid Dracylic acid
Structural Formula	
Molecular Formula	C7H6O2
Molecular Weight (g/mol)	122.12
Appearance and Odour (where available)	A white crystalline powder with a pleasant odour.
SMILES	C(=O)(O)c1ccccc1

Import, Manufacture and Use

Australian

Under previous NICNAS mandatory and/or voluntary calls for information, the chemical has been identified as having an industrial use in Australia; however, specific uses were not reported.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Co-operation and Development Screening information Data Set Initial Assessment Report (OECD SIAR), Galleria Chemica, Substances and Preparations in the Nordic Countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, and United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory:

The chemical has reported cosmetic use in:

- bulking and masking agents; and
- fragrance ingredients, preservatives and pH adjusters.

The chemical has reported domestic use including in:

- adhesives, binding agents;
- cleaning/washing agents;
- colouring agents;
- corrosion inhibitors;
- fillers;
- flame retardants and extinguishing agents; and
- paints, lacquers and varnishes.

The chemical has reported commercial use including in:

- fixing agents;
- lubricants and additives;
- reprographic agents;
- softeners; and
- process regulators for polymerisation processes in production of resins, rubbers and polymers.

The chemical has reported site-limited use including as:

- intermediates; and
- laboratory chemicals.

The chemical has reported non-industrial use including in:

- non−agricultural pesticides and preservatives; and

- pharmaceuticals, milk, food/foodstuff flavourings, plant extracts and nutrients.

A 2010 Personal Care Products industry survey reported the following use concentrations: benzoic acid (0.000002–5 %), sodium benzoate (0.000001–1 %), calcium benzoate (0.002–0.004 %) and potassium benzoate (0.002–0.003 %). No uses of magnesium benzoate were reported in the survey (INCI).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is restricted internationally under the following:

European Union (EU): The use of the chemical in cosmetics is restricted in the EU under Annex V − list of preservatives allowed. It states that benzoic acid and sodium benzoate are safe for use for preservative and non-preservative purposes in cosmetic rinse-off products at a maximum concentration of 2.5 % and in cosmetic oral-care products at a maximum concentration of 1.7 %, and in leave-on products up to 0.5 %.

US Cosmetic Ingredient Review (CIR): The CIR considers the chemical (benzoic acid and its salts) to be safe for use at a maximum allowed concentrations of 5 % (as acid) (INCI).

New Zealand: The chemical is controlled in the New Zealand Cosmetic Products Group Standard − Schedule 7 − list of preservatives allowed in cosmetics. It states that benzoic acid and sodium benzoate are safe for use for preservative and non-preservative purposes in cosmetic rinse-off products at a maximum concentration of 2.5 % and in cosmetic oral-care products at a maximum concentration of 1.7 %, and in leave-on products up to 0.5 %. For other salts of benzoic acid other than listed above, maximum authorised concentrations is 0.5 % (Galleria Chemica).

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

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 5–10 mg/m^3 in different countries such as USA (California, Tennessee), Canada and England.

Health Hazard Information

For most part, benzoic acid and its sodium, magnesium, calcium, ammonium and potassium salts are able to be considered together as a group based on the structural similarity and the physico-chemical properties. A considerable proportion of data for benzoic acid was generated using sodium benzoate because of the low water solubility of benzoic acid at neutral pH. Additionally, for some studies it was not definitely stated whether benzoic acid or its salts were used. Benzoic acid (and its salts) will be present as the benzoate ion under physiological conditions. Therefore, it is reasonable to assume that the results of systemic toxicity studies on benzoic acid will apply to the salts of benzoic acid as well. Benzoic acid differs from its salts in that it is likely to have greater local effects (to the skin, eye and respiratory system) than the salts and these have been considered separately from the benzoate salts.

Toxicokinetics

The chemical is rapidly and almost completely absorbed from the gastrointestinal tract after oral dosing. Studies showed that absorption is based on diffusion of the un-ionised molecule and is dependent on pH. The chemical is metabolised in the liver by conjugation with glycine, resulting in the formation of hippuric acid, which is rapidly excreted via the urine. Because of the high extent of metabolism and elimination, accumulation of the chemical or its metabolites in the body is not expected (ECHA, 2011).

Dermal absorption

The percutaneous absorption in humans has been reported as 14–42.6 % in vivo and 53–99 % in vitro studies. However, 100 % skin absorption was assumed due to the variable results seen in the human studies (SCCNFP, 2002).

Acute Toxicity

Oral

The chemical is of low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats and mice is greater than 2000 mg/kg bw/d.

LD50 in rats ranged from 1700−3040 mg/kg bw/d and in mouse ranged from 1940−2370 mg/kg bw/d. However, the studies that reported the lower LD50s were all pre-guideline studies and no further information was available to critically assess the data. LD50s reported in two reliable studies were 2250 mg/kg bw/d (mice) and 2565 mg/kg bw/d (rats) (OECD, 2004).

Dermal

The chemical exhibits low acute toxicity in animal tests as evidenced by reported dermal LD50 (median lethal concentration) in rats of greater than 2000 mg/kg bw (OECD, 2004).

Inhalation

The chemical exhibits low acute toxicity in animal tests following inhalation exposure. No mortalities or toxic effects were observed in rats and mice with the reported median lethal concentration (LC50) > 12.2 mg/L/4-h (ECHA, 2011; OECD, 2004).

Corrosion / Irritation

Respiratory Irritation

The chemical is not currently classified in HSIS (Safe Work Australia). Available animal and human studies (see **Observation in Humans**) support the classification of the chemical as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia).

Inhalation toxicity of the chemical was evaluated in one rat study (0, 0.025, 0.25 and 1.2 mg/L, 6 h/d 5 d/wk over 4 weeks) using fine benzoic acid dust (see **Repeat dose toxicity − Inhalation**). A reddish discharge around the nostrils was seen in the mid and high dose groups. An increased incidence and intensity of interstitial inflammatory cell infiltrate and interstitial fibrosis (indicating upper respiratory tract irritation) was noted at all doses. Observed histopathological changes were most likely due to a persistent irritating effect of the test substance on the lung. No changes in gross pathology were noted (REACH).

Skin Irritation

The chemical is not currently classified in HSIS (Safe Work Australia). Available animal and human data (see **Observation in Humans)** support the classification of the chemical as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia).

The chemical was irritating (erythema and swelling of the ear lobe) in the guinea pig ear swelling test at ≥ 1%, particularly when dissolved in ethanol, although it was not found irritating in the rabbit (OECD, 2004).

Eye Irritation

The chemical is not currently classified in HSIS. Available animal data support the classification of the chemical as hazardous with the risk phrase 'Risk of serious eye damage' (Xi; R41) in HSIS (Safe Work Australia).

The chemical was highly irritating in rabbit eyes, causing irreversible corneal opacity and chemosis in 2/3 animals, and increasing conjunctival redness severity with white/grey discoloration after 2-day observation. A Draize score of 35 was given based on the effects (REACH). In another rabbit study an irritation score of 65.0/110 was noted. No further details were available from this study (OECD, 2004).

Observation in humans

Several clinical studies have demonstrated the potential of the chemical to cause skin irritation effects in humans.

Positive skin irritant reactions (erythema and oedema) were frequently reported in a number of human studies. The threshold concentrations are strongly dependent on the vehicles (ethanol or petrolatum), skin conditions (scarified/unscarified, dermatitis or urticaria) and application conditions (closed/open patch tests or chamber-scarification tests for skin irritancy) (SCCP, 2005).

Non-immunological contact urticaria has frequently been reported in humans for the chemical. Contact urticarial reactions to the chemical (1 %) were seen in healthy volunteers (SCCP, 2005). Oedematous reaction to the chemical (0.05 %) were also observed in patients during an occlusion test (OECD, 2004).

In humans, cases of respiratory reactions such as rhinitis and asthma have been reported for susceptible persons following oral, dermal or inhalation exposure to benzoic acid (ECHA, 2011).

Sensitisation

Skin Sensitisation

The negative results seen for the chemical from several skin sensitisation animal studies including guinea pig maximisation test (GPMT), Buehler test and local lymph node assay (LLNA) support a conclusion that the chemical is not a skin sensitiser (REACH).

Observation in humans

The chemical did not induce sensitisation in healthy volunteers although some allergic reactions were noted in 34/537 patients with suspected contact dermatitis (at 2 %) (SCCP, 2005) and 9/121 patients with dermatoses and 10/57 patients with chronic urticaria (at 5 %) (ECHA, 2011).

Repeated Dose Toxicity

Oral

Based on the weight of evidence the chemical is not considered to cause serious damage to health by repeated oral exposure (no observed adverse effect level (NOAEL) of 825 mg/kg bw/d). Effects observed at > 1000 mg/kg bw/d included increased mortality, reduced weight gain, and liver and kidney effects (OECD, 2004).

Dermal

Available animal data suggest that the chemical is not likely to cause serious damage to health via repeated dermal exposure.

No treatment-related effects in rabbits at doses of up to 2500 mg/kg bw/d applied 5 d/wk for 3 weeks (OECD, 2004).

Inhalation

Available animal data suggest that the chemical is not likely to cause serious damage to health via repeated inhalation exposure.

The only available rat study for this chemical reported 2/20 mortalities at 1.2 mg/L 6 h/d (5 d/wk over 4 wk). Local reddish discharge around the nostrils and inflammatory cell infiltrates and interstitial fibrosis of the lung secondary to local irritant effects were also observed at ≥ 0.25 mg/L. On the basis of systemic effects, the NOAEC is considered to be > 0.25 mg/L 6 h/d (ECHA, 2011).

Genotoxicity

Based on the weight of the evidence of the in vitro and in vivo genotoxicity data, the chemical is not considered mutagenic or clastogenic.

In vitro data using the reverse mutation assays with various strains of *Salmonella typhimurium* (with and without metabolic activation) and sister chromatid exchange assays (except one equivocal result) were negative. Weak genotoxic effects or equivocal results were observed in most of the chromosome aberration assays in three mammalian cell lines and two of the recombination assays in *Bacillus subtilis* (no further information available, only summary given) (REACH). No genotoxicity was observed in the in vivo cytogenetic, micronucleus, or other assays at either somatic or germ cell level (OECD, 2004).

Carcinogenicity

Based on the avaialble data, the chemical is not considered carcinogenic.

The chemical was not carcinogenic (NOAEL 500 mg/kg bw/d) in a lifetime 3-generation study in rats when given with the diet at doses up to 500 mg/kg bw/d. No increase in the lifetime tumour incidence, clinical abnormalities or histopathological changes were observed (OECD, 2004).

A lifelong study using male/female Swiss Albino mice given the chemical (2 %) continuously in drinking water showed no carcinogenic effect (such as effect on survival or incidence of tumours) (CICAD, 2000).

Reproductive and Developmental Toxicity

No evidence of reproductive or developmental toxicity was observed for the chemical.

A four generation study with benzoic acid was conducted in male and female rats (NOAEL 500 mg/kg bw/d). The first and second generation were fed 0.5 or 1.0 % benzoic acid in the diet (approximately 250 or 500 mg/kg bw/d). The third generation was treated for 16 weeks and generation 4 was treated until breeding. There were no unfavourable side-effects on growth, food utilisation, duration of life, procreation, feeding of the offspring, weight of organs and histological pattern of organs in the 1 % dose group. In the 0.5 % group there was a significant prolongation of lifetime of the rats (OECD, 2004).

In a study to determine the teratologic effects, benzoic acid was administered in a single dose of 510 mg/kg bw/d to Wistar albino rats at day 9 of gestation. The malformations and resorption rates were comparable to those in control animals (NOAEL for maternal toxicity and teratogenicity: 510 mg/kg bw/d) (OECD, 2004).

Other Health Effects

Neurotoxicity

No evidence for neurofunctional abnormalities or histopathological alterations of the central nervous system (CNS) were reported following exposure to doses up to ~500 mg/kg bw/d in rats (ECHA, 2011).

Neurotoxicity and CNS toxicity were assessed in juvenile rats exposed to the diet for up to 35 days at 0, 1.1, and 3 %, corresponding to approximate doses of 0, 825, and 2250 mg/kg bw/d benzoic acid. At day 4, clinical observation showed signs of neurotoxicity in most animals of the highest dose group including ataxia, tremor, excitation, aggressive behaviour and convulsions. However, these changes were deemed secondary to metabolic changes (acidosis, acyl-CoA and ATP depletion). Histological evaluation of the brain showed prominent pathological changes in 2/5 animals treated for 3 days, 18/18 animals treated for 5 days and 13/15 animals with 3 weeks of recovery following the 5 days of exposure. These changes included ischaemic necrosis preferentially of ganglial cells in the stratum granulosum of the fascia dentate and the cortex of the lobus piriformis. No histopathology of the brain or clinical abnormality was noted in any of the animals of the low dose group receiving approximately 825 mg/kg bw/d over 7, 14, or 35 days (ECHA, 2011).

In another developmental neurotoxicity study, the effects of the chemical on activity and behaviour in neonatal and juvenile rats were evaluated. Treatment with 0, 0.1, 0.5, and 1.0 % benzoate in the diet commenced on day 5 of gestation of the parental animals and continued through lactation and after weaning. There were no treatment-related changes in weight or neurotransmitter content for any of 5 analysed brain regions. Consequently, the NOAEL for developmental neurotoxicity in rats was considered as 1 % in the diet, corresponding to approximately 500 mg/kg bw/d (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects associated with the chemical (but not the salts) are skin, eye and respiratory tract irritation. However, no systemic effects were seen with benzoic acid. The salts are expected to exist almost entirely as the benzoate ion under normal physiological conditions and will not have the local irritant properties that arise from the acidity of benzoic acid. Therefore, it is unlikely that any systemic effects will be observed with the salts of benzoic acid.

Public Risk Characterisation

Currently, there are no restrictions on the use of this chemical in Australia. The chemical is reported to be used in cosmetic/domestic products overseas (up to a maximum concentration of 5 % in cosmetics (INCI, 2010), although its use in cosmetic/domestic products in Australia is not known. Taking into account the natural occurrence of benzoic acid (and benzoates) in the environment and the use of these substances in food preservatives and in medications, no concern for the safety of consumers is raised. The likely route of exposure to general public is though dermal use of consumer products containing the chemical. However, in such formulations it is expected that the chemical will be used at very low concentrations and will be buffered to the physiological pH that will mitigate the risk, so no likely harm from the use of cosmetics is expected. Therefore, the risk to the public is considered low.

Occupational Risk Characterisation

Given the critical local health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure (dermal, ocular and inhalation) 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.

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

Considering the available information to indicate low public exposure from this chemical, no regulatory controls are recommended.

Work Health and Safety

The chemical (but not its salts) is recommended for classification and labelling under the current Approved Criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

[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 (dermal, ocular or 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;
- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

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

Obligations under workplace health and safety legislation

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

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

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

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

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

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