Benzoic acid, phenyl ester: Human health tier II assessment

05 February 2016

CAS Number: 93-99-2

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	phenyl benzoate diphenylcarboxylate
Structural Formula	 Structural formula of Benzoic acid, phenyl ester
Molecular Formula	C13H10O2
Molecular Weight (g/mol)	198.22
Appearance and Odour (where available)	White crystals with phenolic coal tar odour.
SMILES	C(=O)(c1ccccc1)Oc1ccccc1

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:

- Galleria Chemica;
- ChemIDplus;

- Registry of Toxic Effects of Chemical Substances (RTECS);
- Personal Care Products Council;
- Handbook of Preservatives, 2004;
- Japan Food Chemical Research Foundation - List of Designated Additives; and
- the European Commission Cosmetic Ingredients and Substances (CosIng) database.

The chemical has reported cosmetic use as:

- a fragrance ingredient; and
- a preservative.

The chemical has reported site-limited use as an intermediate.

The chemical has reported non-industrial use as:

- an agricultural chemical (nematocide); and
- a food flavouring agent.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following:

Cosmetic

- Chile List of Preservatives Allowed in Cosmetic Products;
- European Union (EU) Cosmetics Regulation (EC) No 1223/2009 - Annex V/1a. This preservative may be used in cosmetics and personal care products at a maximum concentration of 0.5% (acid);
- International Fragrance Association (IFRA) Standards—Prohibited (until additional data is available and considered sufficient to support its safe use); and
- Taiwan Standard List of Application and Maximum Levels of Preservatives in Cosmetics.

Other

- Japan Food Sanitation Law - Designated Additives (only for flavouring); and
- Taiwan Scope and Application Standards of Food Additives - Flavouring Agents.

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 available.

Health Hazard Information

There are limited toxicological data available for phenyl benzoate. The main concerns regarding effects on human health are expected to be driven by the products generated by hydrolysis of the ester linkage, either under acidic conditions in the stomach or by esterases throughout the body. The metabolites, benzoic acid (CAS No. 65-85-0) and phenol (CAS No. 108-95-2), have both been previously assessed by NICNAS and have been taken into account in this assessment (NICNASa; NICNASb). The structurally related chemicals, butyl benzoate (CAS No. 136-60-7) and benzyl benzoate (CAS No. 120-51-4) have also been previously assessed, and have been used as read across for endpoint data gaps due to their similar molecular weights, metabolites and uses compared with the chemical (NICNASc; NICNASd).

Toxicokinetics

Limited data are available regarding the absorption and distribution of the chemical, although given its low molecular weight and its high partition coefficient (log K_{ow} = 3.59), the chemical is expected to be absorbed through all routes of exposure. This is also supported by data available for the structurally related chemicals, butyl benzoate and benzyl benzoate (NICNASc; NICNASd). However, due to the presence of esterases throughout all tissues in the body, the chemical is expected to be metabolised and excreted at a similar rate to its absorption at low doses.

Following oral absorption, the chemical is expected to be rapidly absorbed through the stomach and subjected to first-pass metabolism. Hydrolysis of the ester bond is also expected to occur in the acidic conditions of the stomach. Formation of benzoic acid, and in particular phenol, may account for any systemic toxicity. The toxicokinetics of these metabolites have been well documented (NICNASa; NICNASb). Benzoic acid is conjugated to glycine and metabolised to hippuric acid, which is excreted in urine. Phenol is metabolised by sulfonation and glycine conjugation, and also excreted in urine.

Acute Toxicity

Oral

Limited data are available for the chemical. The hazard classification is recommended based on the available data for mice as well as the observed acute toxicity of the metabolites and structurally-similar benzoates (see **Recommendation** section).

In a non-guideline study, the chemical had moderate acute toxicity in mice following oral exposure. The median lethal dose (LD50) in mice was 1225 mg/kg bw. No details of toxic effects were described (ACToR; RTECS).

The chemical is more acutely toxic via the oral route than alkyl benzoates such as butyl benzoate (LD50 3450 mg/kg bw; ACToR), although it has a similar toxicological profile to benzyl benzoate, which has an LD50 in mice of 1.4 mL/kg bw (equivalent to 1568 mg/kg bw) (ACToR). This is expected to be driven by the toxicity of the aromatic alcohols, phenol and benzyl alcohol, which are generated in the acidic conditions of the stomach following ester hydrolysis.

Dermal

No data are available for the chemical.

Benzoate esters are expected to be absorbed through intact skin due to their lipophilicity and small molecular weight, and esterases present in the dermis of the skin can metabolise the chemical, reducing the systemic availability of the chemical through the dermal route. Based on the available data for the metabolites and similar benzoates (NICNASa; NICNASb; NICNASc; NICNASd), the chemical is not expected to be acutely toxic via the dermal route.

Inhalation

No data are available for the chemical.

Based on the available data for the metabolites and similar benzoates (NICNASa; NICNASb; NICNASc; NICNASd), the chemical is not expected to be acutely toxic via inhalation.

Corrosion / Irritation

Skin Irritation

No data are available for the chemical.

A number of notifications to the Classification and Labelling Inventory by industry in the European Union indicated the chemical as irritating to skin (ECHA C&L). However, in the absence of any experimental data, and based on the weight of evidence due to weak local effects observed for similar compounds and negative quantitative structure-activity relationship (QSAR) results, hazard classification for skin irritation is not recommended.

The chemical is expected to be readily absorbed through intact skin and metabolised by esterases in the dermis. Under physiological conditions in the dermis, the metabolites will exist as benzoate and phenoxide species that have significantly reduced local effects compared to the free acid and alcohol, which are irritating and corrosive, respectively (NICNASa; NICNASb). The structurally similar ester compounds, butyl benzoate and benzyl benzoate, have been reported as slightly irritating to the skin (NICNASc; NICNASd). The QSAR modelling for the chemical using the Optimised Approach based on Structural Indices Set-TIssue MEtabolism Simulator (OASIS-TIMES) program gave negative predictions for skin irritation.

Eye Irritation

No data are available.

The QSAR modelling for the chemical using OASIS–TIMES gave negative predictions for eye irritation. However, the chemical structure was out of the applicability domain of the QSAR models, indicating greater uncertainty about the reliability of the negative predictions.

Based on the data available for structurally similar benzoates (NICNASc; NICNASd), the chemical is expected to be at most slightly irritating to eyes.

Sensitisation

Skin Sensitisation

The chemical is not currently classified on HSIS, although it is considered to be a weak to moderate skin sensitiser based on the positive results seen in several local lymph node assays (LLNA). The EC3 value (concentration required to provoke a 3-fold increase in lymph node cell proliferative activity compared with controls) was reported to be 13.6 % (an average calculated from three reported EC3 values) (ICCVAM, 2009). Phenyl benzoate is also a recommended reference standard as a weak sensitiser for OECD TG 429 (OECD, 2010). It is recommended that the chemical be classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS (Safe Work Australia).

In a study equivalent to OECD TG 429, phenyl benzoate was reported to be positive for skin sensitisation in an in vivo mouse LLNA. The mice were administered 0 %, 1 %, 2.5 %, 5 %, 10 % or 25 % (w/v) of the chemical in acetone/olive oil (ratio of 4:1). Stimulation indexes of 0, 2.0, 6.4, 9.3, 8.7 and 11.1 were reported, respectively. The EC3 was reported to be 1.2 %. A similar study with the chemical, at doses of 0 %, 5 %, 10 % and 25 % in the same vehicle, reported positive results for skin sensitisation with stimulation indexes of 0, 2.3, 2.1, and 3.5 respectively, and an EC3 of 20 %. In another study with the chemical, using unreported doses in acetone/olive oil (ratio of 4:1), an EC3 of 19.6 % was reported (ICCVAM, 2009).

Repeated Dose Toxicity

Oral

No data are available for the chemical.

The metabolites (benzoic acid and phenol) are expected to be produced rapidly under repeated dose conditions via the oral route. The metabolite benzoic acid has low repeat dose toxicity (NICNASa), although phenol may cause adverse health effects including tremors and kidney and liver effects (NICNASb). The chronic oral toxicity of phenol is dependent on peak blood concentrations rather than total daily intake of the chemical. Rapid detoxification of the metabolite is expected to occur at low concentrations, which are expected in products containing the chemical as a preservative. The chemical is not expected to cause serious adverse effects following repeated oral exposure except at high doses.

Dermal

No data are available.

Based on the available data for the metabolites and similar compounds (NICNASa; NICNASb; NICNASc; NICNASd), the chemical is not expected to be harmful following repeated dermal exposure at the low concentrations used in cosmetics.

Inhalation

No data are available.

Based on the available data for the metabolites and similar compounds (NICNASa; NICNASb; NICNASc; NICNASd), the chemical is not expected to cause serious damage to health by prolonged exposure through inhalation.

Genotoxicity

No data are available for the chemical. The chemical is expected to have low systemic availability due to its rapid metabolism by esterases. In addition, the available data for the metabolites and structurally similar benzyl benzoate indicate that the chemical is not mutagenic (NICNASa; NICNASb; NICNASc; NICNASd).

The QSAR modelling for the chemical using OASIS–TIMES gave positive predictions for in vivo genotoxicity. However, the chemical structure was out of the applicability domain of the QSAR models, indicating greater uncertainty about the reliability of

the positive predictions. Therefore, QSAR model predictions for the chemical were considered not to outweigh the negative in vivo genotoxicity test results for the metabolites and analogue chemical, when using a weight of evidence approach for genotoxic potential of the chemical.

Carcinogenicity

No data are available. The lack of carcinogenic activity observed for benzoic acid and its butyl and benzyl esters indicates that the chemical is not expected to be carcinogenic (NICNASa; NICNASc; NICNASd). Phenol, the alcohol produced upon metabolism, is also not a carcinogen (NICNASb).

Reproductive and Developmental Toxicity

No data are available for the chemical.

Based on the available data for the metabolites and analogues (NICNASa; NICNASb; NICNASc; NICNASd), the chemical is not expected to cause reproductive or developmental toxicity. The metabolite, phenol, was reported to have developmental effects, although these were shown to be secondary to maternal toxicity (NICNASb).

Risk Characterisation

Critical Health Effects

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

Public Risk Characterisation

Although use in consumer products in Australia is not known, the chemical has reported cosmetic uses overseas at concentrations up to 0.5%, but only as a fragrance compound or a preservative (refer to **Import, Manufacture & Use** section). In these instances, the general public may be exposed to the chemical through the dermal route. However, in such cosmetic formulations, the chemical is expected to be used at low concentrations that are not considered to pose an unreasonable risk to human health.

Occupational Risk Characterisation

During product formulation, 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 systemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and oral 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) (refer to **Recommendation** section).

NICNAS Recommendation

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

Additional regulatory controls could be required should information become available to indicate that the chemical is used in cosmetic products in Australia at concentrations where skin sensitisation is expected.

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
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 industry

Control measures

Control measures to minimise the risk from oral or dermal 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

Ash M and Ash I (2004). Handbook of Preservatives. Synapse Information Resources, Inc. Page 486.

ChemIDPlus, CAS No. 93-99-2 (Diphenylcarboxylate). Accessed November 2015 at http://chem.sis.nlm.nih.gov/chemidplus/rn/93-99-2.

Cosmetics Directive (CosIng). Phenyl Benzoate. Accessed November 2015 at http://ec.europa.eu/consumers/cosmetics/cosing/

European Chemicals Agency (ECHA), Classification and Labelling Inventory. CAS No. 93-99-2. Accessed November 2015 at http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

Galleria Chemica. Accessed November 2015 at https://jr.chemwatch.net/galleria/

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) 2009. Recommended Performance Standards: Murine Local Lymph Node Assay. NIH Publication Number 09-7357. Research Triangle Park, NC: National Institute of Environmental Health Sciences.

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Human Health Tier II assessment for benzoic acid (CAS No. 65-85-0). Australian Government Department of Health. Accessed November 2015 at http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Human Health Tier II assessment for phenol (CAS No. 108-95-2). Australian Government Department of Health. Accessed November 2015 at http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Human Health Tier I Assessment (Cas No. 136-60-7). Accessed November 2015 at http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASd). Human Health Tier I Assessment (CAS No. 120-51-4). Accessed November 2015 at http://www.nicnas.gov.au

OECD (2010). OECD Guideline for the Testing of Chemicals - Skin Sensitization: Local Lymph Node Assay. OECD TG No. 429, 2010. Accessed November 2015 at https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-tg429-2010.pdf

Registry of Toxic Effects of Chemical Substances (RTECS). Phenyl benzoate (93-99-2). Accessed November 2015 at http://ccinfoweb.ccohs.ca/rtecs/search.html

The Japan Food Chemical Research Foundation - List of Designated Additives. Accessed November 2015 at http://www.mhlw.go.jp/english/topics/foodsafety/foodadditives/

United States (US) Environmental Protection Agency's (EPA) Aggregated Computational Toxicology Resource (ACToR). Accessed November 2015 at http://actor.epa.gov/actor/faces/ACToRHome.jsp

United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed November 2015 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

Last update 05 February 2016

Share this page