Benzenemethanol, 4-methoxy-: Human health tier II assessment

01 July 2016

CAS Number: 105-13-5

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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.

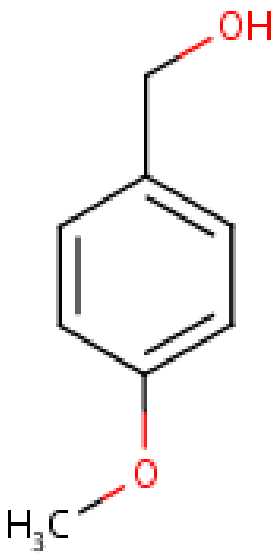
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	anisic alcohol p-methoxybenzyl alcohol anisyl alcohol
Structural Formula	
Molecular Formula	C8H10O2
Molecular Weight (g/mol)	138.17
Appearance and Odour (where available)	white/pale yellow to solid. Sweet powdery odour.
SMILES	c1(OC)ccc(CO)cc1

Import, Manufacture and Use

Australian

The chemical has reported potential domestic use in cleaner/polish products.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier;
- Galleria Chemica;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database;
- the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR);
- 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 US National Library of Medicine's Toxicology Data Network (TOXNET); and
- various international assessments (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2001; the International Fragrance Association (IFRA) Standard (IFRA; 2008; IFRA, 2015); Scognamiglio et al., 2012).

The chemical has reported cosmetic uses, including:

- in perfumes and fragrances; and
- in personal care products.

The chemical has reported commercial use as a photochemical.

The chemical has reported site-limited use as an intermediate in the manufacture of other substances.

The chemical has reported non-industrial uses, including:

- in pharmaceutical manufacture;
- as an insect attractant, insect repellant, and chemosterilant;
- in agricultural products; and
- as a flavouring agent.

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). The chemical may be used in cosmetics and personal care products, but must be specified in the list of ingredients referred to in article 19(1)g when its concentration exceeds:

- 0.001 % in leave on products; and
- 0.01 % in rinse-off products.

Additionally, the International Fragrance Association (IFRA) has restricted the use of the chemical in finished products at concentrations of 0.04-2.5 % depending on the product category (IFRA, 2008; IFRA, 2015).

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

The chemical, also referred to as anisyl alcohol in this assessment, is a substituted benzyl alcohol (benzenemethanol; CAS No. 100-51-6), differing from benzyl alcohol only by the presence of a methoxy group in the *para*- position to the ether group. They are both aryl alkyl alcohols used frequently in fragrance ingredients, producing benzoic acid and hippuric acids as the major metabolites (Belsito et al., 2012; NICNAS). When information for the chemical is limited particularly for local effects, data on benzyl alcohol are used.

Toxicokinetics

The chemical has been identified in animal studies to be metabolised via an oxidation pathway to eventually yield a glycine conjugate which is excreted in the urine. Minor pathways of metabolism include aldehyde conjugation and excretion of mercapturic acid as well as the conjugation of glucuronide conjugate, also excreted in the urine (Belsito et al., 2012).

In a study conducted in rabbits (number and strain not specified), the chemical was administered via gavage at doses of 250 mg/kg bw. The reported metabolites which overestimate the total dose, found 53 % excreted as glucuronic acid conjugate, 19 % as glycine conjugate, 49 % as glucoronic acid conjugate and 32 % as unconjugated methoxybenzoic acid. No other details were provided (Belsito et al., 2012).

In another study conducted in rabbits (six animals; sex and strain not specified), the chemical was administered by gavage at 550 mg/kg. Urine samples were analysed at different time periods up to 24 hours (h). The urinary metabolites identified were substituted benzoic acid (15 %) and substituted hippuric acid (5 %). The remainder of the dose was excreted from the body almost entirely unchanged, thus indicating that the chemical does not bioaccumulate (Scognamiglio et al., 2012; REACH).

Acute Toxicity

Oral

The chemical has low to moderate acute toxicity based on results from animal tests following oral exposure. Median lethal doses (LD50) of 1200-1784 mg/kg bw in rats were reported (Draize et al., 1948; Scognamiglio et al., 2012; REACH). The effects were sufficient to warrant hazard classification.

Several studies conducted in rats and mice, determined the oral LD50 at 1200-1340 mg/kg bw and 1600 mg/kg bw respectively. Limited study details were provided (REACH).

Mice (90 animals/sex/dose) and rats (50/sex/dose) were dosed with the chemical and observed for six days. The LD50 in mice and rats was determined to be 1784 and 1338 mg/kg bw, respectively. Severe dyspnoea prior to death was observed (Draize et al., 1948; Scognamiglio et al., 2012).

In a QSAR prediction conducted using the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Application Toolbox v.2.3, LD50 was estimated at 1266 mg/kg bw (REACH).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rabbits is >2000 mg/kg bw.

In a study conducted in rabbits (4/sex/dose), the chemical was administered at doses of 1250, 2500 and 5000 mg/kg bw with observation for six days. Mortalities were recorded in 1/4 rabbits in the 2500 mg/kg bw dose and 4/4 in the 5000 mg/kg bw dose. The chemical was found to produce slight to moderate erythema and oedema and loss of coordination and muscle tone (Scognamiglio et al., 2012; REACH).

In another study conducted in mice (90 animals/dose), the chemical (100 %) was applied to the skin and the mice were observed for six days. Mortalities were not reported and the LD50 was determined to be >10 000 mg/kg bw (Draize et al., 1948; REACH).

Inhalation

The chemical was predicted by QSAR to be of moderate acute toxicity in animal tests following inhalation exposure. However, this is not sufficient to warrant a hazard classification.

QSAR predictions using the OECD QSAR Application Toolbox v2.3 reported LD50 values in mice and rats of 195 (1019 mg/m^3) and 176 ppm (1070 mg/m^3), respectively (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification.

The chemical (0.5 mL) was applied to albino rats (n=12, 6 with normal and 6 with abraded skin) under occlusive conditions for 24 h. Rats were monitored for 72 h. Moderate irritation including erythema and slight oedema were observed (REACH).

In two studies conducted in mice (ten animals) and rabbits (four animals), the chemical was administered at doses of 1250, 2500 or 5000 mg/kg bw. Moderate irritation (primary irritation score=4) was observed including moderate erythema and oedema (Belsito et al., 2012).

Eye Irritation

No data are available on anisyl alcohol. Benzyl alcohol is recommended for classification as an eye irritant based on results from eye irritation studies in animals. Based on physicochemical similarities, the chemical is expected to be an eye irritant and warrant a hazard classification.

Irritation scores were reported after application of the benzyl alcohol to the eyes of NZW rabbits. The irritation scores were 1-2 for corneal opacity, 0.3-1 for iritis, 2-2.7 for conjunctivitis and 0.7-2.2 for chemosis (NICNAS).

Observation in humans

In an irritation screening study, the chemical at 5 % in petrolatum was applied under occlusion to the skin of human subjects (n=7) for 48 h. The chemical was reported to be not irritating (SCCP, 2012; Scognamiglio et al., 2012; REACH).

In a closed patch study conducted in human subjects (n=465), the chemical was applied under occlusion to the forearm for 24-48 h at concentrations of 0.05-5 % in a cream base solution. Irritation was observed in 11 subjects at concentrations between 0.2 and 1.9 % (Belsito et al, 2012; Scognamiglio et al., 2012; REACH).

Sensitisation

Skin Sensitisation

Based on the weight of evidence available, the chemical is considered to be a skin sensitiser. Although negative results were observed in several non-standard skin sensitisation studies in guinea pigs, positive results were reported in a single local lymph node assay (LLNA) (EC3 is 5.9 %, 1475 µg/cm²).

In a murine local lymph node assay (LLNA) compliant with the principles of good laboratory practice (GLP), the chemical was diluted using 1:3 ethanol:diethyl phthalate and 25 µL was applied to the dorsal surface of each ear of CBA/Ca mice (four females/dose) at doses of 2.5, 5, 10, 25 and 50 % w/v for three consecutive days. Tritiated thymidine (250 µL) was then injected into the tail vein and the auricular lymph nodes were removed 5 h later. The EC3 (estimated concentration that elicits a three-fold increase in lymphocyte proliferation) value was found to be 5.9 % w/v, confirming the chemical as a skin sensitiser (Scognamiglio et al., 2012).

In a study conducted in guinea pigs (6-8/dose), the chemical was applied via an epicutaneous test as the induction at concentrations of 1, 3, 10, 30 or 100 % in water, acetone or petrolatum. The challenge phase involving 5 % of the chemical in the same solvents was then applied through the same route. The subjects did not show skin reactions (Belsito et al., 2012). In another study conducted using the modified Draize method, guinea pigs (four/dose) were treated with an induction dose of the chemical (0.625 %) followed by a challenge dose of 10 % in petrolatum. Skin reactions were not observed (Belsito et al., 2012).

In a study conducted in Hartley guinea pigs (10/sex/dose), an intradermal injection of the chemical (0.1 mL) was administered as the induction phase. Following a two week rest period, the animals were subjected to a modified Draize test, involving an injection of (0.25 %) and topical exposure (10 %) to the chemical. Reactions were observed and scored after 24 h. Results indicated the chemical to be non-sensitising (Scognamiglio et al., 2012; REACH).

Observation in humans

In a human maximisation study, humans (n=25) were pre-treated for 24 h with aqueous sodium lauryl sulfate (SLS) (5%). Following a 10-14 day rest period, subjects were applied with the chemical (3450 $\mu g/cm^2$, 5 %) in petrolatum occlusively to the forearm/back region for five alternate day 48-h periods and monitored for a further 48 h. No positive reactions were recorded (REACH).

Diagnostic patch studies on dermatological patients reported the following results (Belsito et al., 2012):

- no skin reactions in 320 patients with eczema suspected of a contact allergy to fragrances or cosmetics treated with the chemical at 5 %;
- skin reactions in 3/167 patients sensitive to fragrance allergens and suspected of contact dermatitis treated with the chemical at 5 % in petrolatum;
- no skin reactions in 115 patients with contact dermatitis treated with the chemical at 5 % in petrolatum;
- skin reactions in 4/20 patients who are sensitive to perfume treated with the chemical at 5 % in petrolatum; and
- skin reactions in 1/2004 patients with dermatitis treated with the chemical at 1 % in petrolatum.

Cases of dermatitis from contact allergy to the chemical have been reported. In a study conducted on perfume allergic patients (n=20), the subjects were tested with several fragrances. Anisyl alcohol (5% in petrolatum) gave a positive reaction in 5/20 of the subjects (SCCP, 2012).

The IFRA reported a No Expected Sensitisation Induction Level (NESIL) of 1500 µg/cm² based on a human maximisation test and, therefore, classified the chemical as a weak sensitiser (IFRA, 2008; Belsito et al., 2012).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

Based on the limited information available, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a study conducted in mice (strain not specified; 90/sex/dose), the chemical was administered at a dose of 1000 or 2000 mg/kg bw over 90 days. Severe dyspnoea resulted prior to death (REACH).

Inhalation

No data are available.

Genotoxicity

Based on the limited data available, the chemical is not considered to be genotoxic.

No in vivo data are available. The chemical was negative in an in vitro bacterial reverse mutation test in *Salmonella typhimurium* strains TA98, TA100 with and without metabolic activation at doses up to 5000 µg/plate (Scognamiglio et al., 2012; Belsito et al., 2012; REACH).

Carcinogenicity

Available data show no evidence of carcinogenicity of the chemical in mice and rats.

In a study conducted in male B6C3F1 mice (n=32), the chemical was administered repeatedly via gavage at doses of 1, 8, 15 or 22 mg/kg for 12 months. A non-statistically significant increase in haematomas was observed (REACH).

QSAR modelling in rats conducted by the Danish Environmental Protection Agency (EPA) showed the chemical to be non-carcinogenic (REACH).

Reproductive and Developmental Toxicity

No data are available for the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the systemic acute effect of acute toxicity from oral exposure. Local effects include eye irritation and skin sensitisation.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be through the skin, through inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products. Dermal application of products containing the chemical at high concentrations may give rise to allergic responses.

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 and ocular 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

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.

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, the chemical should be considered for listing in the *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. Matters to be taken into consideration include:

- the known uses of the chemical. Although there is limited information to confirm that the chemical is currently used in cosmetic and domestic products in Australia, there is reported to be widespread use (CIUCUS, 2011) in cosmetic and domestic products overseas at concentrations up to 2.5 % (SCCP, 2012);
- skin sensitisation has been reported at concentrations >5 %;
- use of the chemical was recommended at 0.04 - 5 % for a range of cosmetic products (Belsito et al., 2012); and
- restrictions on the cosmetic uses overseas. The restrictions on the use of this chemical in cosmetic products in the European Union and IFRA 48th ammendment (see **International restrictions**) are considered appropriate to mitigate the risk.

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)
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 oral, dermal and occular 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:

- 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 help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

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

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

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

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

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