1,6-Octadien-3-ol, 3,7-dimethyl-, 2-aminobenzoate: Human health tier II assessment

12 December 2019

CAS Number: 7149-26-0

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.

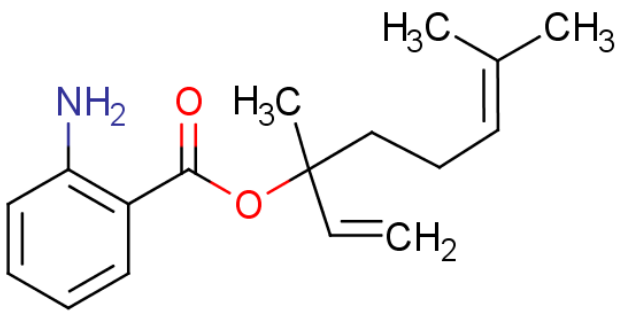
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	linalyl anthranilate anthranilic acid,1,5-dimethyl-1-vinyl-4-hexenyl ester 3,7-dimethyl-1,6-octadien-3-ol 2-aminobenzoate linalyl o-aminobenzoate 1,5-dimethyl-1-vinylhex-4-enyl 2-aminobenzoate
Structural Formula	
Molecular Formula	C17H23NO2
Molecular Weight (g/mol)	273.38
Appearance and Odour (where available)	Colourless to pale yellow clear oily liquid with a sweet orange-like flavour. Insoluble in water.
SMILES	C(=O)(c1c(N)cccc1)OC(C)(C=C)CCC=C(C)C

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; the European Commission Cosmetic Ingredients and Substances (CosIng) database; and the International Fragrance Association (IFRA) Transparency List.

The chemical has cosmetic and domestic uses in perfumes or as a fragrance ingredient (SCCNFP, 2000).

The chemical has reported non-industrial use as food flavouring/additive (JECFA, 2006).

The calculated total systemic exposure for the chemical is 0.00034 mg/kg/day assuming 100 % dermal absorption when used as a fragrance ingredient in products (Api et al., 2019).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the United States (US) Drug Enforcement Administration (DEA) List I and II Regulated Chemicals under the entry 'Anthranilic acid, its esters, and its salts' (Galleria Chemica). The metabolite anthranilic acid is a drug precursor for the synthesis of methaqualone.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Limited data are available for linalyl anthranilate (CAS No. 7149-26-0). As the chemical is expected to be hydrolysed in vivo to form linalool (CAS No. 126-91-0) and anthranilic acid (CAS No. 118-92-3), data for these metabolites are considered suitable analogues for systemic effects.

Toxicokinetics

Following oral exposure, linalyl esters readily hydrolyse in vivo by carboxylesterases or tissue esterases to linalool and the corresponding carboxylic acids (JECFA, 2006). The hydrolysis products then conjugate with glucuronic acid and are excreted in urine. Studies for linalyl acetate indicate that linalool is available for systemic circulation following absorption (NICNASa).

The carboxylic metabolite, anthranilic acid, is a metabolite of the amino acid tryptophan that occurs naturally in the body and is present in urine together with other metabolites of tryptophan in humans. It has been suggested that anthranilic acid is hydroxylated at the 3- and 5-positions in rabbits and at the 3-position in rats. The hydroxylated derivatives of anthranilic acid, including 3-hydroxyanthranilic acid, have been evaluated for their potential carcinogenic effects (NICNASb).

Acute Toxicity

Oral

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

The reported median lethal dose (LD50) is 4250 mg/kg bw in rats. No details on sub-lethal effects are available (Galleria Chemica).

Dermal

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

The reported LD50 is >5000 mg/kg bw in rabbits. No details on sub-lethal effects are available (Galleria Chemica).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not a skin irritant in rabbits and humans; therefore, hazard classification is not warranted.

The undiluted chemical did not cause skin irritation in rabbits when applied under occlusion to intact or abraded skin for 24 hours (Opdyke, 1979). No further details are available.

Eye Irritation

No data are available.

Observation in humans

In a 48-hour closed-patch test study, the chemical tested on human subjects at a concentration of 8 % in petrolatum did not produce skin irritation (Opdyke, 1979).

Sensitisation

Skin Sensitisation

Based on the available data on the human maximisation study and information on the metabolites and analogues, the chemical is not considered to be a potent skin sensitiser. In the absence of more comprehensive information, hazard classification is not warranted.

The chemical could hydrolyse in skin to linalool which is a known contact allergen following auto-oxidation. Available data for linalyl acetate indicate auto-oxidation into a potent contact allergen. However, other linalyl esters (linalyl isobutyrate and linalyl propionate) were not sensitising when tested at 8 % in guinea pigs (NICNASa).

The other metabolite, anthranilic acid, was not a skin sensitiser based on a mouse local lymph node assay (LLNA) using up to 50 % concentration of anthranilic acid (NICNASb).

The lack of skin sensitisation potential is supported by the lack of skin sensitisation alerts from OECD quantitative structure activity relationship (QSAR) prediction (QSAR Toolbox 4.2).

Observation in humans

In a human maximisation test, the chemical was tested at a concentration of 8 % in petrolatum on 25 volunteers. No sensitisation was observed (Api et al., 2019; Opdyke, 1979).

Repeated Dose Toxicity

Oral

Based on the available data and information on the metabolites, the chemical is not considered to cause serious damage to human health from oral exposure.

The metabolite linalool was not considered to cause serious damage to health from repeated oral exposure. In a 28-day repeat dose oral toxicity study using coriander oil (72.9 % linalool), Sprague Dawley (SD) rats were treated at doses of 160, 400 or 1000 mg/kg bw/day. The no observed adverse effect level (NOAEL) was 160 mg/kg bw/day based on histological effects in the liver and kidney at 400 mg/kg bw/day (NICNASc).

The metabolite anthranilic acid was not considered to cause serious damage to health following repeated oral exposure. In a subchronic study conducted as part of a long-term carcinogenicity study, male SD rats and male Swiss mice (5/dose) received anthranilic acid in the diet at concentrations of 1000, 5000, 10000, 25000, or 50000 ppm (equivalent to ~90, 450, 900, 2250 or 4500 mg/kg bw/day for rats; and ~200, 1000, 2000, 5000 or 10000 mg/kg bw/day for mice), 7 days/week for 45 days followed by an additional 45 days of observation. Body weights were reduced by 11 and 17 % in rats receiving 25000 and 50000 ppm, respectively. Body weights in mice were not affected. Based on the data, NOAEL is determined to be 4500 and 10000 mg/kg bw/day for rats and mice, respectively (NICNASb).

Dermal

No data are available.

The metabolite linalool did not cause systemic toxicity effects at doses up to 1000 mg/kg bw/day in a 91-day repeat dose dermal toxicity study in SD rats. The NOAEL was 250 mg/kg bw/day for local effects (NICNASc).

No data are available for anthranilic acid.

Inhalation

No data are available.

Genotoxicity

Based on the in vitro data for the chemical and data for the metabolites, the chemical is not expected to be genotoxic.

The chemical was negative in a bacterial reverse mutation assay (OECD Test Guideline (TG) 471) in *Salmonella typhimurium* strains TA98, 100, 1535 and 1537 with and without metabolic activation (S9) at concentrations up to 666 µg/plate (TOXNET).

Available in vitro data for linalool did not indicate mutagenic potential. Linalool was not clastogenic in an in vivo mouse micronucleus test (NICNASc).

Anthranilic acid showed negative results in gene mutation studies in bacteria. The chemical was positive in some mutation and clastogenicity studies in mammalian cells, but it tested negative for clastogenicity in vivo (NICNASb).

Linalyl anthranilate and its metabolites present alerts for mutagenicity based on their molecular structures as profiled by the OECD QSAR Toolbox v4.2. The presence of a primary aromatic amine present an opportunity for potential interaction with deoxyribonucleic acid (DNA) molecules through nitrenium ion formation. However, the mostly negative results from available in vitro and in vivo studies of the parent compound and metabolites indicate that linalyl anthranilate is not likely to be genotoxic at the low concentrations expected in consumer products.

Carcinogenicity

No data are available.

The metabolites linalool and anthranilic acid are not considered to be carcinogens (NICNASc; NICNASb).

Reproductive and Developmental Toxicity

No data are available.

The metabolites linalool and anthranilic acid are not considered to be reproductive or developmental toxicants (NICNASc; NICNASb).

Risk Characterisation

Critical Health Effects

No critical health effects for risk characterisation were identified for the chemical.

Public Risk Characterisation

Although use in Australia is not known, the chemical is reported to be used in cosmetic and/or domestic products overseas. The chemical belongs to class I based on the Cramer decision tree for anticipated Threshold of Toxicological Concern (TTC) (i.e. “substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity”) (EFSA, 2008). The calculated systemic exposure of the chemical based on 100 % dermal absorption from cosmetic products is below the TTC value of 0.03 mg/kg bw/day. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, exposure might 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 lack of critical health effects, the chemical is unlikely to pose an unreasonable risk to workers when adequate control measures to minimise exposure are implemented.

Based on the available data, the lack of hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers’ health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Work Health and Safety

The chemical is not recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Advice for industry

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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