Fragrances with low worldwide production volumes: Human health tier III assessment

26 October 2018

CAS Number: 879-67-4, 52844-21-0, 2257-09-2, 6379-73-3, 67801-43-8, 7779-72-8.

Chemical Name on the Inventory	CAS Number
Phenol, 2-methoxy-4-methyl-, acetate	879-67-4
Cyclohexenecarboxaldehyde, 2,6,6-trimethyl-	52844-21-0
Benzene, (2-isothiocyanatoethyl)-	2257-09-2
Benzene, 2-methoxy-1-methyl-4-(1-methylethyl)-	6379-73-3
Benzenepropanoic acid, .beta.-oxo-, 4-methylphenyl ester	67801-43-8
Propanoic acid, 2-oxo-, 3-methylbutyl ester	7779-72-8

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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 III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

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

Disclaimer

Acronyms & Abbreviations

Synopsis

Under the IMAP framework, it was determined that further work is required to assess the extent of use and determine appropriate risk management for chemicals with limited data availability identified as used in fragrances.

The IMAP Human Health Tier II Assessment report for 'Chemicals with limited data availability that are used in fragrances' can be accessed online and contains assessment information that remains valid (NICNAS). New or updated information is included in the Tier III Human Health Assessment report in the relevant sections.

This Tier III assessment focuses on 6 chemicals with reported low volume of use following stakeholder consultation and updated international exposure information in 2018. The Tier II and Tier III reports should be read together.

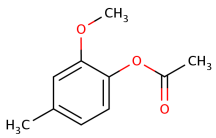
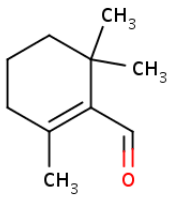
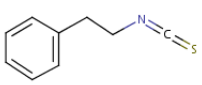
Rationale for Tier III Assessment

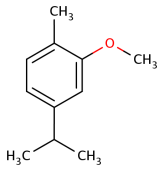
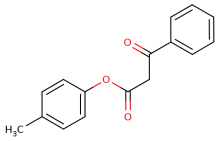
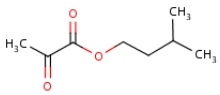
The chemicals have reported use in fragrances overseas, but no specific use has been identified in Australia. Based on recent consultation with industry and current international exposure information from publicly available sources, some chemicals are assessed to have reported low volume of use or potentially no longer in use in fragrances.

In the Tier II assessment, the critical health effects identified were potential skin sensitisation and systemic long-term effects (genotoxicity and carcinogenicity) based on the structural alerts of the chemicals using Quantitative Structure–Activity Relationship (QSAR) modelling analysis. No significant new toxicological data have become available since the Tier II assessment.

This Tier III assessment was conducted in order to evaluate all available exposure data to determine if the chemicals are still being used in fragrances or if there are any other uses apart from fragrances; and if risk management controls for occupational and public health are required.

Chemical Identity

Chemical name on the Inventory and Synonyms	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Phenol, 2-methoxy-4-methyl-, acetate phenol, 2-methoxy-4-methyl-, 1-acetate 2-methoxy-p-cresol acetate 2-methoxy-p-tolyl acetate	879-67-4		C12H10O	170.21
Cyclohexenecarboxaldehyde, 2,6,6-trimethyl- alpha(beta)-cyclocitral 2,6,6-trimethylcyclohexenecarbaldehyde	52844-21-0		C10H16O	152.2354
Benzene, (2-isothiocyanatoethyl)- phenethyl isothiocyanate isothiocyanic acid, phenethyl ester 1-(2-isothiocyanatoethyl)benzene	2257-09-2		C9H9NS	163.243

Chemical name on the Inventory and Synonyms	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Benzene, 2-methoxy-1-methyl-4-(1-methylethyl)- 5-isopropyl-2-methylanisole methylcarvacrol carvacryl methyl ether	6379-73-3		C11H16O	164.246
Benzenepropanoic acid, .beta.-oxo-, 4-methylphenyl ester hydrocinnamic acid, .beta.-oxo, p-tolyl ester p-tolyl 3-oxo-3-phenylpropionate	67801-43-8		C16H14O3	254.284
Propanoic acid, 2-oxo-, 3-methylbutyl ester isopentyl pyruvate pyruvic acid, isopentyl ester isoamyl pyruvate	7779-72-8		C8H14O3	158.1

Import, Manufacture and Use

Since the Tier II assessment of these chemicals, recent industry-provided information and online searches of products that could contain the chemicals are provided in Table 1. Updated information has been obtained from databases including the International Fragrance Association (IFRA) transparency list (IFRA, 2016) and the United States (US) Toxic Substances Control Act (TSCA) inactive list (US EPA, 2018).

Table 1: Indicative use and reported Volume of Use (VoU) as a fragrance ingredient

CAS Number and Chemical name on the Inventory	Uses identified from the Tier II assessment (NICNAS)	Additional indicative use and other information that have become available since the Tier II assessment	Volume of Use (VoU) as a fragrance ingredient (IFRA, 2018)
879-67-4 **Phenol, 2-methoxy-4-methyl-, acetate**	Fragrance use based on the 2011 IFRA transparency list	TSCA inactive (US EPA, 2018) No other known reported uses	No reported global VoU Possibly no longer in use in cosmetics (IFRA, 2017)
52844-21-0 **Cyclohexenecarboxaldehyde, 2,6,6-trimethyl-**	Fragrance use based on US EPA ACToR	A mixture of isomers, alpha(beta)-cyclocitral which is also grouped commercially with CAS No. 432-25-7 under the generic name ‘cyclocitral’ (PubChem; Leffingwell & Associates, 2015; JFCRF, 2018) Not reported for use in fragrance in cosmetic databases (CosIng; Personal Care Products Council; IFRA, 2016) TSCA inactive (US EPA, 2018) No other known reported uses	‘Cyclocitral’ (CAS No. 432-25-7) is reported to have ‘perfuming use’ on CosIng and IFRA transparency list with a global VoU of up to 1 kg

CAS Number and Chemical name on the Inventory	Uses identified from the Tier II assessment (NICNAS)	Additional indicative use and other information that have become available since the Tier II assessment	Volume of Use (VoU) as a fragrance ingredient (IFRA, 2018)
2257-09-2 **Benzene, (2-isothiocyanatoethyl)-**	Fragrance use based on the 2011 IFRA transparency list, site-limited use as intermediate, non-industrial use as food flavourings and/or food additives	Antitumour therapeutic use, and site-limited research and development purposes (Sigma-Aldrich, Pubchem). Although the chemical has reported 'perfuming use' (CosIng), it is noted that the chemical has a strong 'sulfurous type' odour (Good Scents; ScienceDirect).	Global VoU up to 100 kg and Asia-Pacific (includes Australia) VoU up to 10 kg
6379-73-3 **Benzene, 2-methoxy-1-methyl-4-(1-methylethyl)-**	Fragrance use based on the 2011 IFRA transparency list, domestic use in cleaning/washing products, non-industrial use as food flavourings and/or food additives	Fragrance use (IFRA, 2016) Discontinued for sale (Sigma-Aldrich)	Global VoU up to 10 kg and no known Asia-Pacific (includes Australia) VoU
67801-43-8 **Benzenepropanoic acid, .beta.-oxo-, 4-methylphenyl ester**	Fragrance use based on the 2011 IFRA transparency list	No reported use in fragrances and in household products in cosmetic databases (CosIng; Personal Care Products Council; US Household Products Database; IFRA, 2016) No other known reported uses	Global VoU up to 10 kg and no known Asia-Pacific (includes Australia) VoU
7779-72-8 **Propanoic acid, 2-oxo-, 3-methylbutyl ester**	Fragrance use based on US EPA ACToR and non-industrial use as food flavourings and/or food additives	No reported use in fragrances and in household products in cosmetic databases (CosIng; Personal Care Products Council; US Household Products Database; IFRA, 2016) Reported use as a food additive (Galleria Chemica) Discontinued for sale (Sigma-Aldrich)	No data available

Exposure

Public Exposure

The public could be exposed to the chemicals in this group if they are used in fragrances or in other cosmetic products in Australia. The extent of current global and Australian usage and volumes (refer to Table 1) indicate that the chemicals may no longer be used in fragrances or other cosmetic products. If the chemicals are in use, these are expected to be at very low concentrations.

Health Hazard Information

Fragrance ingredients may pose a concern in relation to their potential skin sensitisation, mutagenicity and carcinogenicity hazards. Since the time of the Tier II assessment of these chemicals, no animal data have become available on skin sensitisation and carcinogenicity.

The following in vitro genotoxicity data have become available for benzene, 2-methoxy-1-methyl-4-(1-methylethyl) (CAS No. 6379-73-3) (Api et al., 2017):

- Negative in a bacterial reverse mutation assay [conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 476] with and without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA administered the chemical in dimethyl sulfoxide (DMSO) at concentrations up to 5000 mg/plate.
- Not clastogenic in a micronucleus test (conducted according to OECD TG 487) with and without metabolic activation in human peripheral blood lymphocytes administered the chemical in DMSO at concentrations up to 2000 mg/mL.
- Negative in a BlueScreen assay with and without metabolic activation. No other details provided.

No additional genotoxicity data are available for the other chemicals in the group.

QSAR modelling predictions as presented in the Tier II assessment of these chemicals remain unchanged since the publication of this report.

Risk Characterisation

Critical Health Effects

The critical health effects identified have not changed from the Tier II assessment [potential skin sensitisation and systemic long-term effects (genotoxicity and carcinogenicity)].

Public Risk Characterisation

While uses in fragrances or other cosmetic products in Australia were not identified, the chemicals are reported to be used in fragrances or other cosmetic products overseas. The general public could be exposed through the skin or inhalation when using cosmetic products containing the chemicals.

Based on the low volume of use for the chemicals, public exposure to the chemicals is not expected to be at a concentration high enough to cause systemic long-term effects or local effects.

Therefore, based on the available information, risk is not considered to be unreasonable.

Occupational Risk Characterisation

Based on the low volume of use for the chemicals, significant occupational exposure to the chemicals is not expected.

Therefore, based on the available information, risk is not considered to be unreasonable.

NICNAS Recommendation

No further assessment is required for the chemicals in this group. However, if any information becomes available to indicate significant use and consumer exposure in Australia, further assessment may be undertaken to characterise changes to public and occupational risks and to determine the appropriate controls if necessary.

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