Tonalide and related polycyclic musks: Environment tier II assessment

25 November 2016

CAS Registry Numbers: 21145-77-7, 1506-02-1, 88-29-9, 17610-24-1, 774-55-0.

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.

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Acronyms & Abbreviations

Grouping Rationale

This Tier II assessment considers the environmental risks associated with the industrial uses of four organic substances that share a common bicyclic acetyltetralin ring system. The risk assessment of these substances has been conducted as a group because they all have applications as synthetic polycyclic musks.

Synthetic musks, which include nitromusks, polycyclic musks and macrocyclic musks, are primarily used as ingredients in fragrance mixtures. Polycyclic musks are widely used, and various international studies have identified the bicyclic acetyltetralin musk, tonalide (CAS RNs 21145-77-7 and 1506-02-1), and/or the tricyclic musk, galaxolide (CAS RN 1222-05-5), in almost all household products with added fragrances that have been sampled (eg. Reiner and Kannan, 2006).

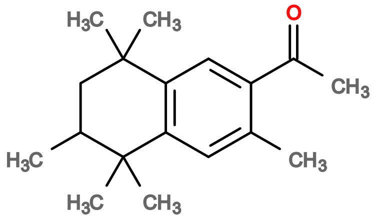
Fragrance ingredients are ubiquitous components of numerous classes of formulated products including cosmetics, personal hygiene products, and various household cleaning agents. These products are released into sewers nationwide as a normal part of their use pattern. The use of polycyclic musks in these products therefore has significant potential to result in environmental exposure through a common pathway involving release of the chemicals in the treated effluents and biosolids produced by sewage treatment plants.

The Tier I assessment of tonalide indicated that it was potentially a persistent, bioaccumulative and toxic (PBT) substance and, therefore, of high environmental concern. This Tier II assessment includes further refinement of the risk characterisation for tonalide and a more in-depth assessment of the available environmental hazard and exposure information for this substance. This assessment also includes a review of the available environmental hazard and exposure information for three closely related acetyltetralin polycyclic musks which are listed on the Inventory and therefore available for industrial uses, including as fragrance ingredients, in Australia.

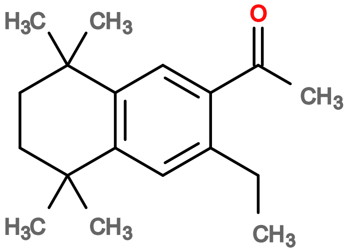
Chemical Identity

The chemical, ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)-, has been assigned two CAS RNs by the Chemical Abstracts Service (21145-77-7 and 1506-02-1). These two CAS RNs are numerical identifiers for the same chemical substance and both are listed on the Inventory. This assessment provides findings that are applicable to the chemical identified by either CAS RN on the Inventory.

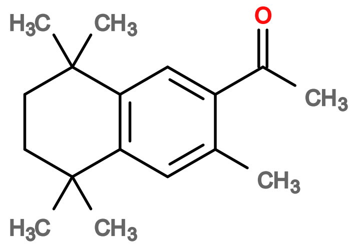
The stereochemistry of tonalide is not specified by the Chemical Abstracts Service chemical name. The technical form of tonalide used industrially is a racemic (equal) mixture of the two configurational stereoisomers of this chemical (ECB, 2008).

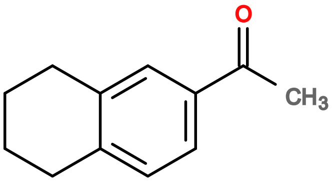
CAS RNs	21145-77-7 1506-02-1
Chemical Name	Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)-
Synonyms	tonalide fixolide acetylhexamethyltetrahydronaphthalene (AHTN) 7-acetyl-1,1,3,4,4,6-hexamethyltetralin
Structural Formula	
Molecular Formula	$C_{18}H_{26}O$
Molecular Weight (g/mol)	258.40
SMILES	Cc1cc2c(cc1C(C)=O)C(C)(C)CC(C)C2(C)C

This chemical is a structural isomer of tonalide (CAS RNs 21145-77-7 and 1506-02-1).

CAS RN	88-29-9
Chemical Name	Ethanone, 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-
Synonyms	versalide acetylethyltetramethyltetralin (AETT) 7-acetyl-6-ethyl-1,1,4,4-tetramethyltetralin
Structural Formula	
Molecular Formula	$C_{18}H_{26}O$
Molecular Weight (g/mol)	258.40
SMILES	CCc1cc2c(cc1C(C)=O)C(C)(C)CCC2(C)C

CAS RN	17610-24-1
Chemical Name	Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-
Synonyms	7-acetyl-1,1,4,4,6-pentamethyltetralin
Structural Formula	

	
Molecular Formula	$C_{17}H_{24}O$
Molecular Weight (g/mol)	244.37
SMILES	Cc1cc2c(cc1C(C)=O)C(C)(C)CCC2(C)C

CAS RN	774-55-0
Chemical Name	Ethanone, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)-
Synonyms	6-acetyltetralin floranton
Structural Formula	
Molecular Formula	$C_{12}H_{14}O$
Molecular Weight (g/mol)	174.24
SMILES	CC(=O)c1ccc2CCCCc2c1

Physical and Chemical Properties

The measured physical and chemical property data for tonalide were retrieved from the European Union Risk Assessment Report (EU RAR) for tonalide, and from the databases included in the OECD QSAR Toolbox (ECB, 2008; LMC, 2013). The values for key chemical properties of other chemicals in this group were calculated using standard quantitative structure-property relationships (QSPR) (US EPA, 2008):

Chemical	tonalide (exp.)	versalide	6-acetyltetralin
Physical Form	solid	solid	-
Melting Point	55.1°C	46.5°C (exp.)	58.9°C (calc.)
Boiling Point	326°C	335.5°C (calc.)	273.2°C (calc.)
Vapour Pressure	0.0682 Pa (at 25°C)	0.025 Pa (calc.)	0.52 Pa (calc.)
Water Solubility	0.91–1.31 mg/L	0.09 mg/L (calc.)	45.9 mg/L (calc.)
Ionisable in the Environment?	no	no	no
log K_{ow}	5.4–5.7	6.42 (calc.)	3.64 (calc.)

Experimental physical and chemical property data are limited for versalide, and not available for 7-acetyl-1,1,4,4,6-pentamethyltetralin and 6-acetyltetralin.

Tonalide is a moderately volatile substance that is slightly soluble in water. The high measured values for the octanol-water partition coefficient (K_{ow}) determined by several methods indicate that this neutral organic chemical is lipophilic and that it will therefore have a strong tendency to partition from water into lipids.

Versalide has similar physical and chemical characteristics to tonalide based on calculated values for properties such as water solubility, octanol-water partitioning and vapour pressure. This is consistent with expectations for two structural isomers. The calculated water solubility for versalide may be an underestimate of the solubility of this substance based on the underestimation of the water solubility for tonalide using QSPRs (water solubility = 0.35 mg/L). Hence, the measured water solubility for tonalide is taken to be indicative of the water solubility of versalide in this assessment.

Based on calculated values, 7-acetyl-1,1,4,4,6-pentamethyltetralin has comparable properties to tonalide and versalide (e.g. log K_{ow} = 5.93). The unsubstituted end-member of this group, 6-acetyltetralin, is relatively more water soluble, less lipophilic, and more volatile than these other substances.

Import, Manufacture and Use

Australia

No specific Australian use, import, or manufacturing information has been identified.

International

Polycyclic musks have a musky odour and are used as ingredients in fragrance formulations due to their strong odour and fixative properties, whereby they act to bind to other substances and to surfaces such as fabrics and skin (Reiner and Kannan, 2006). Fragrance formulations containing polycyclic musks are typically used in detergents, fabric softeners and conditioners, cleaning agents, furniture polish, and air fresheners. They are also used in cosmetics and personal hygiene products, such as soaps, shampoos, perfumes and deodorants (Reiner and Kannan, 2006; Rimkus, 1999).

In a survey of household commodities conducted in 2006 in the United States of America (USA), tonalide was present in 48% of perfumes, 29% of body lotions/creams, 75% of deodorants, 14% of shower gel/shaving creams, 33% of hair products and 31% of sanitation products (Reiner and Kannan, 2006). Tonalide is the second highest volume polycyclic musk in terms of global production: a total of 247 tonnes of tonalide was used in Europe in 2004; in North America in 2011, reported use volumes were in the range of 100 to 150 tonnes (Biomonitoring California, 2013; ECB, 2008).

Versalide was previously used as a synthetic musk in cosmetic applications. However, following discovery of the neurotoxic properties of the chemical in 1979, the two large scale producers of versalide ceased production (Rietschel and Fowler, 2008). The use of the chemical in cosmetics was prohibited in the EU in 2000, and the International Fragrance Association (IFRA) recommends that the chemical is not used (European Commission, 2000; IFRA, 2014). However, monitoring of contaminants of emerging concern in San Francisco Bay found versalide in approximately 8% of mussels sampled in 2010, which may indicate some ongoing uses of this fragrance chemical (Klosterhaus, et al., 2013).

Tonalide and 6-acetyltetralin are listed on the IFRA Transparency List, which identifies chemicals used as fragrances by member companies (IFRA, 2015). Versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin are not listed.

Environmental Regulatory Status

Australia

The use of the chemicals in this group is not subject to any specific national environmental regulations.

United Nations

None of the chemicals in this group are currently identified as a Persistent Organic Pollutant (UNEP, 2001), ozone depleting substance (UNEP, 1987), or hazardous substance for the purpose of international trade (UNEP & FAO, 1998).

OECD

Tonalide was identified as a High Production Volume (HPV) chemical by the OECD in 2004. This indicates that the chemical was used at more than 1000 tonnes per annum in at least one member country or region. Tonalide was sponsored for assessment under the Cooperative Chemicals Assessment Programme (CoCAP) by the Netherlands, and assessed at the 28th Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM 28) in 2009. The SIDS Initial Assessment Profile (SIAP) found that the chemical may present a hazard for the environment (OECD, 2009).

The other substances in this group have not been sponsored for assessment under CoCAP (OECD, 2013).

Canada

Tonalide was categorised as not Persistent (P), not Bioaccumulative (not B), and Inherently Toxic to the Environment (iT_E) by Environment Canada during the categorisation of the Domestic Substances List (DSL) and was not prioritised for further assessment (Environment Canada, 2013).

Versalide was deleted from the DSL in 2008 and added to the Non-Domestic Substances List (NDSL) (Environment Canada, 2015; Government of Canada, 2008).

Of the remaining two chemicals in this group, 6-acetyltetralin is on the DSL and was categorised as not P, not B and not iT_E, and 7-acetyl-1,1,4,4,6-pentamethyltetralin is on the NDSL.

European Union

All chemicals in this group were pre-registered under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation. However, only tonalide has undergone the full registration process (ECHA, 2014a; 2016)

Tonalide was listed on the fourth Priority Substances List under the superseded Existing Substances Regulation (ESR) (ECHA, 2014b). The associated risk assessment (EU RAR), published in 2008, concluded that for all environmental compartments no additional information and/or testing is needed, and no additional risk reduction measures are required (ECB, 2008).

United States of America

All chemicals in this group are listed on the inventory of chemicals manufactured or processed in the USA, as published under the *Toxic Substances Control Act 1976* (TSCA) (US EPA, 2015). A pre-manufacture notice (PMN) received by the US EPA in 1986 for 6-acetyltetralin indicates that this substance was to be imported for use as a perfume ingredient at 100 to 200 kg per year.

Environmental Exposure

Available international use data indicate that tonalide is frequently used as a component of synthetic fragrance oils, which are incorporated into a wide variety of consumer products, including cosmetics, air fresheners, personal hygiene products, and various household cleaning agents (ECB, 2008). The formulation of similar products on the Australian market is assumed to not differ significantly from those found internationally. Therefore, tonalide is expected to be found in a wide range of household and commercial products available for use in Australia.

Chemicals used in cosmetics, personal hygiene and cleaning products are typically released to sewers in waste water as a normal part of their use pattern. Depending on degradation and partitioning processes of chemicals in sewage treatment plants (STPs), some fraction of the quantity of chemicals in waste water entering STPs can be emitted to the air compartment, to rivers or oceans in treated effluent, or to soil through application of biosolids to agricultural land. Based on the high lipophilicity of tonalide, and taking into account standard removal efficiencies, up to approximately 80% of the total quantity of this chemical entering a typical STP may be removed by adsorption to sludge, which may be applied to land as biosolids (Struijs, 1996). Hence, emissions of tonalide to both environmental surface waters and soils are considered as part of this assessment.

The assumed use of tonalide as a component of fragrance ingredients in consumer products available in Australia is supported by a recent domestic environmental monitoring study which identified this chemical in the treated effluent of STPs (Tang, et al., 2013). No domestic environmental monitoring data for the remaining chemicals in this group were identified for this assessment. However, if used as fragrance ingredients these chemicals are expected to be released to the environment by pathways that are similar to those identified for tonalide.

Environmental Fate

Partitioning

Tonalide is expected to remain in soil, or partition between water and sediment, when released from industrial uses.

Tonalide is a neutral organic chemical that is only slightly soluble in water and moderately volatile (LMC, 2013). The measured Henry's Law constant for tonalide is 37.1 Pa-m^3/mol (at 25°C) (ECB, 2008), which indicates that tonalide is moderately volatile from water and moist soil.

Tonalide is also a highly lipophilic chemical, which typically indicates that it will have low mobility in soil. This expectation is supported by measured organic-carbon normalised soil adsorption coefficients (K_{oc}) for tonalide in the range 5012 to 13 490 L/kg (ECB, 2008). Based on these measured values for K_{oc}, tonalide is considered to be immobile in soil.

The partitioning behaviour of tonalide in other systems such as the sludge-water and suspended organic matter-water systems is more complex. Based on studies reviewed in the EU RAR, the partitioning of tonalide in the sludge-water system is non-linear with concentration and not reversible. The partitioning of tonalide to sludge is apparently less efficient at lower overall concentrations of the chemical (ECB, 2008). This could result in an overestimation of the removal efficiency of tonalide from waste water in STPs by sorption processes and an increase in the uncertainty in estimated concentrations of this chemical in treated effluents.

Calculations with a standard multimedia partitioning (fugacity) model assuming equal and continuous distributions to air, water and soil compartments (Level III approach) predict that tonalide will mainly partition to the soil compartment (85.1%), with minor partitioning to the water compartment (8.75%) and the sediment compartment (5.6%) (US EPA, 2008). However, with sole release to the water compartment, it is predicted that tonalide will predominantly partition to water (60.3%), but with significant partitioning to the sediment compartment also expected (38.6%) (US EPA, 2008).

The estimated partitioning behaviour of the remaining chemicals in this group is similar to the partitioning of tonalide with the exception that 6-acetyltetralin is predicted to partition almost exclusively to the water compartment when this chemical is only released into water.

Degradation

Tonalide is persistent in soil and is only slowly degraded in water.

Tonalide is not readily or inherently biodegradable in studies conducted in accordance with OECD Test Guidelines (TG) 301B and 302C, with both studies finding 0% degradation over 28 days. These findings have added significance because the tests were modified to enhance the potential for biodegradation by increasing the bioavailability of tonalide (through the use of ultra-sonication, solvents or surfactants) and by the use of adapted sludge microorganisms (ECB, 2008). Versalide is also reported to undergo 0% degradation over 28 days in a ready biodegradability study conducted according to OECD TG 301B (Büttner, et al., 2007).

Although tonalide does not undergo measurable biodegradation in typical screening tests, it has been shown to undergo primary biodegradation under simulated STP operating conditions and in river water. A Continuous Activated Sludge test conducted with ^{14}C-labelled tonalide demonstrated that 87.5% of the applied tonalide was removed with nearly half of the removal due to biotransformation and most of the remainder removed through sorption. The effluent contained 12.5% of applied radioactivity in the form of the parent chemical and polar metabolites. In a die-away test with freshly collected activated sludge and ^{14}C-labelled tonalide, the primary half-life for the parent chemical was determined to be in the range 12 to 24 hours with most of the parent chemical converted to polar metabolites in 20 days. A similar study with ^{14}C-labelled tonalide and activated sludge in river water also demonstrated biotransformation of the parent chemical to polar metabolites with an overall half-life of nine days. The same study also showed substantial volatilisation of the test substance from water (40.4%) over 28 days (ECB, 2008).

The fate of tonalide has been investigated in a number of differing soil types and under a variety of conditions. The dissipation half-lives determined in some field and laboratory studies are greater than 180 days, which demonstrates that tonalide can persist in soil for long periods. In a recent field study conducted in China, a dissipation half-life in soil for tonalide of 336 days was determined after a single application of biosolids. The biosolids, which contained 1.4 mg/kg of tonalide, were obtained from a municipal sewage sludge treatment plant (Chen, et al., 2014b). In another study conducted under laboratory conditions, 75% of the chemical remained in the biosolids-amended soils after 259 days (Müller and Böhmer, 2006).

No studies on the degradation of versalide in soil have been identified.

No studies on the biodegradation of 7-acetyl-1,1,4,4,6-pentamethyltetralin or 6-acetyltetralin in water or soil were identified for this assessment. Both substances are predicted to be not readily biodegradable according to standard quantitative structure-activity relationships (QSAR) (US EPA, 2008).

Some partitioning to the air compartment of all chemicals in this group is expected based on their volatility and their function as fragrances in industrial products. Based on the results of calculations with standard QSPRs, all of the chemicals in this group are predicted to undergo rapid photo-oxidation by hydroxyl radicals in the troposphere (half-life ≤ 1 day) (US EPA, 2008). This prediction is supported by the findings of studies on the gas phase reactions of hydroxyl radicals with structurally related fragrance chemicals such as galaxolide which show that the measured and estimated rates of reaction are within a factor of 1.3 to 1.5 (ECB, 2008).

Bioaccumulation

Tonalide has a moderate potential to bioconcentrate in aquatic organisms.

The available experimental data for tonalide show that it has a moderate bioconcentration potential in fish, with a study conducted in accordance with OECD TG 305E reporting a bioconcentration factor (BCF) of 1320 L/kg wet weight in *Lepomis macrochirus*. The reported bioconcentration factor was based on total radioactivity and includes multiple identified polar metabolites of tonalide. It was concluded that the BCF for the parent chemical alone was 597 L/kg wet weight. The study also found evidence of depuration of tonalide in the form of polar metabolites (ECB, 2008). As discussed in the European Risk Assessment for tonalide, additional studies have found tonalide wet weight BCFs within the same range for other fish species.

No evidence has been identified in this assessment to indicate that tonalide biomagnifies through the aquatic food chain. Tonalide has been identified in the maternal serum, umbilical cord serum, breast milk and adipose tissue of humans (Kang, et al., 2010; Rimkus and Wolf, 1996). However, it is noted that humans may have direct exposure to this chemical from the use of cosmetic and personal care products, and these findings are therefore not necessarily indicative of transfer of tonalide through the food chain.

No experimental bioaccumulation data are available for the other chemicals in this group. Therefore, the log K_{ow} parameter has been used to provide an indication of the bioaccumulation potential of these chemicals. The calculated log K_{ow} values for versalide (6.42) and 7-acetyl-1,1,4,4,6-pentamethyltetralin (5.93) both significantly exceed the domestic categorisation threshold for bioaccumulation hazards (log $K_{ow} \geq 4.2$). In addition, calculations with standard quantitative structure-bioconcentration relationships show that both chemicals have estimated bioconcentration factors in fish from upper trophic levels of 2948 and 3033 L/kg, respectively (US EPA, 2008). These calculated BCF values exceed the domestic categorisation threshold for bioaccumulation (BCF ≥ 2000 L/kg) and both chemicals are therefore considered to have high bioconcentration potential in fish. It is noted that the calculated BCF for tonalide (3496 L/kg) also exceeds the domestic categorisation threshold and that it is possible that the bioconcentration potential of versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin are overestimated.

For 6-acetyltetralin, both the calculated log K_{ow} value (3.64) and the estimated BCF in upper trophic level fish (205 L/kg) are below the respective categorisation thresholds. This chemical is, therefore, not considered to be a bioaccumulation hazard.

Transport

Tonalide may undergo long-range transport.

Environmental monitoring has identified tonalide in pristine environmental areas, including remote alpine lakes and glaciers in Switzerland (Bogdal, et al., 2009; Schmid, et al., 2007). As these environments do not typically receive direct anthropogenic outputs, these data suggest the potential input of polycyclic musks to these sites by wet and gaseous deposition after transport of the chemicals through the atmosphere from distant emission sources (Schmid, et al., 2007).

Predicted Environmental Concentration (PEC)

The predicted environmental concentrations for tonalide are based on available domestic and international monitoring data for tonalide in waste water effluents, biosolids and soils.

Tonalide has been measured in the Katherine River in the Northern Territory at concentrations between 3.1 and 6.2 nanograms per litre (ng/L). However, since the Katherine River is one of the least polluted rivers in Australia these levels are not considered representative of typical surface water concentrations (Schult, 2012).

The predicted environmental concentration for tonalide can be estimated assuming an annual introduction volume of 100 tonnes per annum as outlined in the IMAP Framework. If standard exposure modelling for the release of chemicals to surface waters in STP effluents is used, the concentration of tonalide in rivers is estimated to be 13.6 µg/L (EPHC, 2009; NICNAS, 2013; Struijs, 1996).

However, international monitoring data indicate this may overestimate typical environmental concentrations. Several studies conducted in Europe between 1994 and 2004 found tonalide in STP effluent at concentrations between 0.02 and 5.8 µg/L, but the reported median effluent concentrations were in a more narrow range between 0.6 and 2.2 µg/L (ECB, 2008). Similar concentrations of tonalide were also detected in Canadian and American STP effluents (ECB, 2008). Tonalide concentrations of 0.1 µg/L were measured in the effluent from one STP in Australia in a study conducted in 2010 (Tang, et al., 2013).

Taking available environmental monitoring data into account, the maximum concentration of tonalide in river water in Australia is estimated to be 2 µg/L.

Tonalide levels measured in biosolids from multiple wastewater treatment plants around the world range from 0.032 to 427 mg/kg, and the average concentration is 9.3 mg/kg. Following the application of biosolids containing tonalide to land, the concentration of tonalide predicted in soil is 0.001–13.1 mg/kg (Langdon, et al., 2010). The few reported concentrations of tonalide in soil available internationally are in the range of 0.002 to 0.058 mg/kg dry weight (dw). These soil concentrations depend on the concentration of tonalide in the applied biosolids, the application rate of biosolids to soils (including repeat applications), and the rate of dissipation in soil (Chen, et al., 2014a; Chen, et al., 2014b).

Based on available information, global use of polycyclic musks in fragrance ingredients is dominated by tonalide and galaxolide. Hence, if the remaining chemicals in this group are used as fragrance ingredients domestically, they are only expected to be used in small volumes resulting in limited environmental emissions. The environmental concentrations of the remaining chemicals in this group have, therefore, not been estimated using default introduction volumes.

Environmental Effects

Effects on Aquatic Life

Tonalide is expected to cause toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

Tonalide is only slightly soluble in water and the reliability of aquatic toxicity data can, therefore, be difficult to interpret. This is particularly the case for short-term (acute) studies conducted under static exposure conditions, and studies which only report nominal exposure concentrations of the test substance. However, it is acknowledged that chemicals can cause toxic effects within the range of their reported solubility limits, and underestimation of hazard is to be avoided (EPHC, 2009). Therefore, in this assessment, aquatic ecotoxicity values within an order of magnitude above the reported water solubility limit have been considered as reliable for the purposes of hazard characterisation.

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for freshwater and marine model organisms across three trophic levels exposed to tonalide were reported in a review of personal care products or in the Registration Dossier for the chemical under the European Union REACH legislation (Brausch and Rand, 2011; REACH, 2013)

Taxon	Endpoint	Method

Taxon	Endpoint	Method
Fish	96 h LC50 = 1.49 mg/L	Experimental *Lepomis macrochirus* (Bluegill) OECD TG 204
Invertebrate	48 h LC50 = 0.71 mg/L	Experimental *Acartia tonsa* (Marine copepod)
Algae	72 h EC50 > 0.84 mg/L	Experimental *Pseudokirchneriella subcapitata* (Green algae) OECD TG 201

The toxicity values reported above were derived from studies in which co-solvents and dispersants were used to maintain exposure concentrations of tonalide.

No experimental data for the acute aquatic toxicity of the remaining chemicals in this group were identified. However, all four chemicals are categorised as non-polar (or baseline) toxicants and they are, therefore, all expected to have acute toxic effects that are largely determined by their respective potential to partition into biological membranes from water (US EPA, 2008).

The partitioning of versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin into membranes is expected to be comparable to that of tonalide based on their similar log K_{ow} values and very similar molecular structures. Hence, tonalide is potentially suitable as an analogue for the acute toxic effects of these two chemicals. However, the measured toxicity values for tonalide have been obtained from studies using co-solvents and dispersants to maintain exposure concentrations, and the read-across of toxicity values for tonalide to the other two chemicals may not be reliable. Moreover, calculations of the acute toxicity of all three chemicals with standard QSARs show that they may not be sufficiently soluble to demonstrate toxic effects at saturation (US EPA, 2012). The acute aquatic toxicity of versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin is, therefore, currently uncertain.

The water solubility of 6-acetyltetralin is higher than the other chemicals in the group and the reliability of the calculated acute toxicity values for this chemical is not limited by water solubility. Based on standard QSAR models for non-polar toxicants, aquatic invertebrates are the most sensitive taxonomic group to acute effects of this chemical with a calculated 48 h LC50 for daphnids of 3.2 mg/L (US EPA, 2012).

Chronic toxicity

The following no-observed-effect-concentration (NOEC) values for freshwater model organisms across three aquatic trophic levels exposed to tonalide were reported in a review of personal care products, in the Registration Dossier for the chemical under the European Union REACH legislation, or in the EU RAR for tonalide (Brausch and Rand, 2011; ECB, 2008; REACH, 2013):

Taxon	Endpoint	Method

Taxon	Endpoint	Method
Fish	34 d NOEC = 0.035 mg/L	Experimental *Danio rerio* (Zebrafish) OECD TG 210 Intermittent flow-through Morphology change observed
Invertebrates	21 d NOEC = 0.196 mg/L	Experimental *Daphnia magna* (Water flea) OECD TG 202 – Part II Inhibition of reproduction observed
Algae	72 h NOEC = 0.40 mg/L	Experimental *Pseudokirchneriella subcapitata* (Green algae) OECD TG 201 Decreased growth rate observed

The toxicity values reported above for tonalide were derived from studies in which co-solvents and dispersants were used to maintain exposure concentrations of this slightly soluble chemical.

The potential for tonalide to cause toxic effects in some organisms through inhibition of multixenobiotic resistance transporters has been discussed (Luckenbach and Epel, 2005). However, insufficient data are currently available to evaluate the potential for this effect to cause adverse outcomes in organisms exposed to tonalide and related polycyclic musks in the environment.

There are no suitable data available to evaluate the chronic effects of other chemicals in this group on aquatic organisms.

Effects on Sediment-Dwelling Life

Tonalide can cause toxic effects in sediment-dwelling organisms.

The following no-observed-effect-concentration (NOEC) values for three model organisms exposed to tonalide in sediments were reported in the EU RAR for tonalide (ECB, 2008):

Taxon	Endpoint	Method

Taxon	Endpoint	Method
Midge	28 d NOEC = 101 mg/kg dw	Experimental *Chironomus riparius* (Harlequin fly) OECD TG 218 Decreased development rate observed
Amphipod	28 d NOEC = 18.2 mg/kg dw	Experimental *Hyalella azteca* (Scud) Mortality observed
Worm	28 d NOEC = 7.1 mg/kg dw	Experimental *Lumbriculus variegatus* (Blackworm) Growth inhibition observed

The toxicity values reported above for tonalide were derived from studies in which pre-conditioned artificial sediment (2% organic carbon) was spiked with tonalide on a quartz sand carrier. The toxicity values were calculated from measured exposure concentrations and they are presented on a common dry weight of sediment basis (ECB, 2008).

No suitable data were identified to evaluate the effects of other chemicals in this group on sediment-dwelling life.

Effects on Terrestrial Life

Tonalide and versalide can cause toxic effects in terrestrial organisms.

Chronic ecotoxicity values have been obtained for the springtail *Folsomia candida* and the earthworm *Eisenia fetida* exposed to tonalide in studies conducted according to ISO test guidelines. Both tests were carried out in standard soil with 10% added organic matter (Sphagnum peat). A 28 d NOEC of 45 mg/kg dw soil was obtained for *F. candida* and an 8 week NOEC of 105 mg/kg dw soil was obtained for *E. fetida*. Reproductive toxicity was observed in both tests (ECB, 2008).

Versalide has neurotoxic effects in terrestrial organisms. Wistar rats treated with versalide demonstrated behavioural abnormalities, including gait disturbance and ataxia, and dermal and organ discolouration. These abnormalities were attributed to myelin degeneration of the peripheral and central nervous systems (Akasaki, et al., 1990; Opdyke, 1979).

Predicted No-Effect Concentration (PNEC)

Fish were found to be the most sensitive taxon to chronic toxic effects of tonalide on aquatic life. Therefore, the results from the 34 d fish toxicity test with zebrafish were used to derive a PNEC for water. The PNEC for tonalide in water is calculated to be 0.35 µg/L, based on the 34 d NOEC of 0.035 mg/L and an assessment factor of 100. A conservative assessment factor of 100 was selected as although chronic ecotoxicity data are available across three aquatic trophic levels, tonalide has moderate bioaccumulation potential in fish.

The soil-dwelling Collembolla, *F. candida*, was more sensitive to the toxic effects of tonalide in soil than earthworms. Therefore, the toxicity value for *F. candida* was used to derive a PNEC for soil. Following the approach used in the EU RAR, the NOEC for

F. candida was first normalised to a soil organic content of 3.4% (ECB, 2008). An assessment factor of 50 was then applied to the adjusted NOEC for tonalide in soil (15.3 mg/kg dw) to obtain the PNEC for soil (0.31 mg/kg dw) (EPHC, 2009).

Categorisation of Environmental Hazard

The categorisation of the environmental hazards of ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)- (tonalide); ethanone, 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)- (versalide); ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)- (7-acetyl-1,1,4,4,6-pentamethyltetralin); and ethanone, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)- (6-acetyltetralin) according to domestic environmental hazard thresholds is presented below (EPHC, 2009; NICNAS, 2013):

Persistence

Persistent (P). Based on the slow dissipation rates for tonalide in soil this chemical is categorised as Persistent. The remaining chemicals are categorised as Persistent based on slow ultimate degradation in water predicted with standard QSARs and the lack of measurable biodegradation of versalide in a ready biodegradability screening test.

Bioaccumulation

Tonalide

Not Bioaccumulative (Not B). Based on measured BCFs less than 2000 L/kg in fish, tonalide is categorised as Not Bioaccumulative.

Versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin

Bioaccumulative (B). Based on high log K_{ow} values and calculated BCFs in fish greater than 2000 L/kg, both chemicals are conservatively categorised as Bioaccumulative.

6-Acetyltetralin

Not Bioaccumulative (Not B). Based on a log K_{ow} value and calculated BCF in fish that are both below the respective categorisation thresholds, this chemical is categorised as Not Bioaccumulative.

Toxicity

Tonalide

Toxic (T). Based on a measured acute toxicity value less than 1 mg/L and a chronic toxicity value below 0.1 mg/L, this chemical is categorised as Toxic.

Versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin

Uncertain (Uncertain T). There is currently insufficient information to conclude whether these two chemicals have comparable toxicity to tonalide. The toxicity of these chemicals is therefore categorised as Uncertain.

6-Acetyltetralin

Not Toxic (Not T). Based on calculated acute aquatic toxicity values greater than 1 mg/L, this chemical is categorised as Not Toxic.

Summary

Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)- (tonalide) is categorised as:

- P
- Not B
- T

Ethanone, 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)- (versalide) and ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)- (7-acetyl-1,1,4,4,6-pentamethyltetralin) are categorised as:

- P
- B
- Uncertain T

Ethanone, 1-(5,6,7,8-tetrahydro-2-naphthalenyl)- (6-acetyltetralin) is categorised as:

- P
- Not B
- Not T

Risk Characterisation

Water

The below risk quotient (RQ = PEC ÷ PNEC) for the riverine compartment has been calculated based on the PEC and PNEC values determined for tonalide:

PEC (µg/L)	PNEC (µg/L)	RQ
2.00	0.35	5.71

An RQ greater than 1 indicates that industrial uses of tonalide may pose an unreasonable risk to the environment, as environmental concentrations may exceed levels that cause harmful effects.

It is noted that this calculation may overestimate the risks to the aquatic compartment since the median concentration of tonalide in surface waters measured internationally is 0.088 µg/L (Brausch and Rand, 2011). If this median exposure concentration for tonalide is taken to be representative of surface waters in Australia, an RQ of 0.25 is obtained which would indicate a generally low risk to the aquatic compartment.

However, concentrations of tonalide in STP effluents have been reported in the range 1 to 2 µg/L in multiple studies carried out internationally (ECB, 2008). An effluent concentration of 2 µg/L tonalide poses potential risks because river flows may consist entirely of effluent released from STPs in the drier parts of Australia (EPHC, 2009).

Soil

The below risk quotients for the soil compartment have been calculated for two scenarios involving applications to soil of biosolids contaminated with different concentrations of tonalide:

	PEC (mg/kg dw)	PNEC (mg/kg dw)	RQ
Case A	0.06	0.31	0.19
Case B	13	0.31	41.9

A predicted concentration for tonalide in soil of 0.06 mg/kg dw was calculated for Case A based on an average concentration of the chemical in biosolids of 9.3 mg/kg and assuming a single application of biosolids to soil using standard agricultural practices in Australia (EPHC, 2009). In this scenario, the concentration of tonalide in soil is below the PNEC following a single application of biosolids and the risks to the soil compartment are, therefore, expected to be low.

However, it is noted that repeat applications of biosolids to land do occur, and that tonalide is persistent in soil. If no dissipation of tonalide is assumed to occur and repeated applications of biosolids with this average tonalide concentration are made over a ten year period at the same application rate (EPHC, 2009), the cumulative concentration of the chemical in soil would exceed the PNEC (RQ = 1.9), which may pose a risk to soil organisms.

The risks are significantly higher for Case B in which maximum measured concentrations for tonalide in biosolids are assumed and where a higher application rate of biosolids to soil is used (40 tonnes per hectare versus 10 tonnes per hectare). In this scenario, the concentration of tonalide in soil exceeds the PNEC by more than a factor of 40 and a single application of biosolids could have significant potential for adverse impacts on the soil compartment.

Sediment

The risks posed by the release of tonalide to the sediment compartment have not been characterised in this assessment. However, it is noted that this chemical is toxic to sediment-dwelling organisms and there may be risks to aquatic life where tonalide accumulates in the sediment compartment.

Key Findings

The chemicals in this group have industrial applications as fragrance compounds. Tonalide is known to be used in significant volumes internationally in a wide range of consumer products, including cosmetics, personal hygiene and cleaning products. A similar use pattern is assumed in comparable products available in Australia. This assumption is supported by environmental monitoring studies which have measured tonalide concentrations in a river and in the effluent of a sewage treatment plant in Australia.

Tonalide is persistent in soil and also undergoes slow ultimate biodegradation in water. Although it is a highly lipophilic neutral organic chemical it has only moderate bioaccumulation potential in fish. Tonalide has high chronic toxicity to fish and it is also toxic to soil and sediment-dwelling organisms. The estimated concentrations of tonalide in STP effluents in Australia exceed the PNEC for this chemical and there is a potential risk to aquatic life in rivers. A potential risk to the soil environment has also been identified based on the application to soil of biosolids contaminated with tonalide.

Tonalide is not a PBT substance according to domestic environmental hazard criteria.

The remaining chemicals in this group are not expected to have significant industrial uses as fragrance ingredients in Australia. These chemicals are not currently a priority for further assessment under the IMAP framework as they are not anticipated to be emitted to the environment in significant quantities. However, two of the chemicals in this group, versalide and 7-acetyl-1,1,4,4,6-pentamethyltetralin, have been categorised as persistent (P) and bioaccumulative (B) in this assessment. Chemicals with these hazard characteristics are of environmental concern and further assessment of the risks they pose may be required if there is evidence of significant industrial uses in Australia.

The remaining chemical in this group, 6-acetyltetralin, is not a PBT substance according to domestic environmental hazard criteria and is not prioritised for any further assessment.

Recommendations

It is recommended that tonalide be considered for assessment of environmental concerns at Tier III level under the IMAP framework.

Environmental Hazard Classification

In addition to the categorisation of environmental hazards according to domestic environmental thresholds presented above, the classification of the environmental hazards of ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)- (tonalide) according to the third edition of the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (GHS) is presented below (UNECE, 2009):

Hazard	GHS Classification (Code)	Hazard Statement
Acute Aquatic	Category 1 (H400)	Very toxic to aquatic life
Chronic Aquatic	Category 1 (H410)	Very toxic to aquatic life with long lasting effects

The acute aquatic hazards of tonalide were classified based on the ecotoxicity data presented in this assessment. The long-term aquatic hazards of tonalide were classified based on the available chronic aquatic toxicity data taking into account the non-rapid degradation of this chemical in aquatic ecosystems (UNECE, 2009).

Insufficient data were identified in this assessment to reliably classify the aquatic hazards of the remaining chemicals in this group.

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