Nitromusks: Environment tier II assessment

27 November 2014

CAS Registry Numbers: 81-14-1, 81-15-2, 83-66-9, 116-66-5.

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 closely related nitromusks:

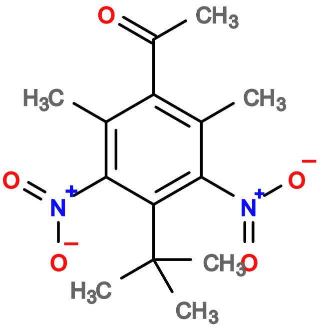
Ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- (Musk ketone)
Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (Musk xylene)
Benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (Musk ambrette)
1*H*-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (Musk moskene)

The risk assessment of these chemicals has been conducted as a group because all four substances are structurally related nitrobenzene compounds which find industrial use as synthetic musk fragrances. These fragrance compounds have applications in cosmetics and household cleaning products, which are released into sewers as a normal part of their use in domestic and industrial applications. The use of nitromusks in these products has significant potential to result in environmental exposure through a common pathway involving releases of the chemicals in the treated effluents and biosolids produced by sewage treatment plants.

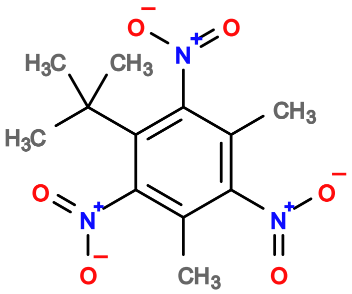
In addition, the Tier I assessments for all four chemicals highlighted potential persistence, bioaccumulation and toxicity (PBT) hazard characteristics, which indicate high environmental concern. Similar concerns have been identified internationally, and some regulatory agencies have implemented risk management measures for nitromusk compounds.

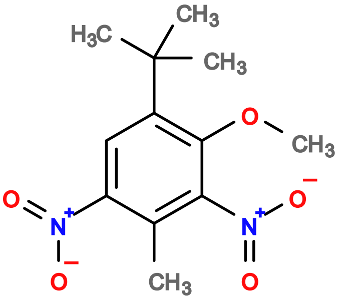
Based on these considerations, the chemicals in this group are each expected to present generally similar environmental concerns for industrial uses in Australia.

Chemical Identity

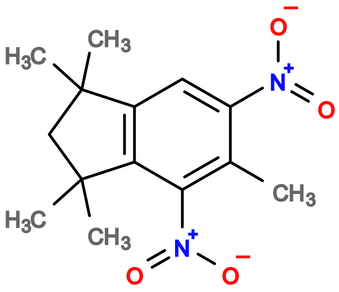
CAS RN	81-14-1
Chemical Name	Ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-
Synonyms	Musk ketone
Structural Formula	
Molecular Formula	$C_{14}H_{18}N_2O_5$
Molecular Weight (g/mol)	294.30
SMILES	C(C)(=O)c1c(C)c([N+](=O)[O-])c(C(C)(C)C)c([N+](=O)[O-])c1C

CAS RN	81-15-2
Chemical Name	Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-
Synonyms	Musk xylene Musk xylol
Structural Formula	

	
Molecular Formula	$C_{12}H_{15}N_3O_6$
Molecular Weight (g/mol)	297.26
SMILES	C(C)(C)(C)c1c([N+](=O)[O-])c(C)c([N+](=O)[O-])c(C)c1[N+](=O)[O-]

CAS RN	83-66-9
Chemical Name	Benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro-
Synonyms	Musk ambrette
Structural Formula	
Molecular Formula	$C_{12}H_{16}N_2O_5$
Molecular Weight (g/mol)	268.27

SMILES	C(C)(C)(C)c1c(OC)c([N+](=O)[O-])c(C)c([N+](=O)[O-])c1

CAS RN	116-66-5
Chemical Name	1*H*-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-
Synonyms	Musk moskene Moskene
Structural Formula	
Molecular Formula	$C_{14}H_{18}N_2O_4$
Molecular Weight (g/mol)	278.30
SMILES	C1(C)(C)c2c(C(C)(C)C1)c([N+](=O)[O-])c(C)c([N+](=O)[O-])c2

Physical and Chemical Properties

The physical and chemical property data for musk ketone and musk xylene were retrieved from the databases included in the OECD QSAR Toolbox, the European Union Risk Assessment Reports for the two chemicals, or calculated using EPISuite (ECB, 2005a; 2005b; LMC, 2013; US EPA, 2008).

Chemical	Musk ketone	Musk xylene
Physical Form	Solid	Solid

Melting Point	135°C (exp.)	112°C (exp.)
Boiling Point	250°C decomposes (exp.)	270°C decomposes (exp.)
Vapour Pressure	0.005 Pa (exp.)	8.48×10^{-5} Pa (calc.)
Water Solubility	0.460 mg/L (exp.)	0.150 mg/L (exp.)
Ionisable in the Environment?	No	No
log K_{ow}	4.6 (exp.)	4.9 (exp.)

Limited experimental physical and chemical property data are available for musk ambrette and musk moskene. Available data suggest similar properties to musk ketone and musk xylene. Musk ambrette is slightly more soluble in water (water solubility = 0.79 mg/L), and is predicted to have a moderate to high octanol-water partition coefficient (K_{ow}; log K_{ow}= 4.17) (Schramm, et al., 1996; US EPA, 2008). A measured log K_{ow} of 4.0 for musk ambrette was published by Schramm *et al.* (1996). Musk moskene is soluble in water at a rate of 0.046 mg/L, and has a measured log K_{ow} of 5.3 (OSPAR Commission, 2004).

Import, Manufacture and Use

Australia

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

International

Nitromusks have a musky odour and are used as fragrance ingredients. They are used as base notes in fragrance formulations due to their strong scent and fixative properties, whereby they act to bind other substances to surfaces such as fabrics and skin. The fragrances are typically used in detergents, fabric softeners and conditioners, cleaning agents, air fresheners and cosmetic products, such as soaps, shampoos and perfumes (OSPAR Commission, 2004; RPA, 2008). Many companies, including large multinational fragrance producers, have voluntarily phased out use of most chemicals in this group (IFRA, 2006; 2014a ; 2014b). However, available recent data indicate that at least three members of this group are still in use internationally.

Musk ketone is used in cleaning and washing agents, surface treatments, and lubricants and additives (Nordic Council of Ministers, 2014). Use in cosmetics is also expected, although this use is subject to restrictions in the European Union (European Commission, 2008; 2014a ; 2014b; OSPAR Commission, 2004). The chemical was reported to be used in over 100 products in three Nordic countries in 2012 (Nordic Council of Ministers, 2014).

Recent regulatory changes have resulted in a phase out of use of musk xylene in the European Union (ECHA, 2014a; 2014b). However, the chemical was previously imported in significant volumes for various uses (OSPAR Commission, 2004; RPA, 2008).

By 2008, bulk import volumes were estimated to have decreased to approximately 25 tonnes per annum (from 174 tonnes in 1992) for use at less than ten manufacturing sites due to public concerns regarding the chemical (RPA, 2008). Data available for three Nordic countries show the chemical was used in over 60 products in 2012 (Nordic Council of Ministers, 2014). Previous estimates had suggested that 80% of the imported bulk chemical was used in detergents, cleaning products and fabric softeners, with the remaining 20% used in cosmetic products such as perfumes and shampoos (RPA, 2008).

In 2003 it was estimated that approximately 20 tonnes of musk ketone and 70 tonnes of musk xylene were used in the United States of America (USA) per annum (US NLM, 2013). Musk xylene has been identified as in use in air freshener products in the USA (FMA, 2009). Use of musk ketone and musk xylene has also been recently identified in China. A study published in 2011 found musk ketone to be present in over half of the 158 Chinese household products tested, with musk xylene detected in one in five of the tested products (Taylor, et al., 2014).

Use of musk ambrette in cosmetic products has been prohibited in the European Union and Canada for a number of years (European Commission, 2008; 2014b; 2014c; Health Canada, 2014). Nevertheless, the chemical was reported to be in use in Denmark in 2012 (Nordic Council of Ministers, 2014). It has previously been estimated that approximately 45 tonnes of this chemical was used in the USA per annum (US NLM, 2013).

The use of musk moskene in cosmetics has been prohibited in the European Union since 2000 (European Commission, 2008; 2014b; 2014d). A Canadian survey found that the chemical was not used at a volume greater than 100 kg in 2005 (Environment Canada, 2013a).

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

Musk ketone and musk xylene were identified as High Production Volume (HPV) chemicals by the OECD in 2004. This indicates that these chemicals were used at more than 1000 tonnes per annum in at least one member country or region (OECD, 2004).

Both musk ketone and musk xylene have been sponsored for assessment under the Cooperative Chemicals Assessment Programme (CoCAP) by the Netherlands. The 14th Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM 14) found that both chemicals were candidates for further work (OECD, 2002a; 2002b).

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

Canada

Musk xylene was categorised as Persistent (P), not Bioaccumulative (not B), and not Inherently Toxic to the Environment (not iT_E) by Environment Canada during the Categorization of the Domestic Substances List (DSL). This chemical was not prioritised for further assessment. Musk ketone and musk ambrette were categorised as P, not B, and iT_E. These chemicals have not yet undergone further assessment (Environment Canada, 2013b ; 2013c).

Musk moskene was categorised as P, B, and iT_E by Environment Canada during the Categorization of the DSL (Environment Canada, 2013b). A subsequent Screening Assessment concluded that the chemical was not being used at a volume of more than 100 kg per annum, and the application of the Significant New Activity (SNAc) provisions of the *Canadian Environmental Protection Act, 1999* was recommended (Environment Canada, 2013a). A SNAc notice was published in July 2013. Approval is required before the chemical can be introduced into Canada for a new use at a volume greater than 100 kg per annum (Government of Canada, 2013).

European Union

All chemicals in this group have been pre-registered, but have not yet undergone the full registration process, under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation (ECHA, 2014d).

Musk ketone and musk xylene were listed on the third Priority Substances List under the superseded Existing Substances Regulation (ESR) (ECHA, 2014c). When the REACH legislation came into effect, musk xylene was identified as a Substance of Very High Concern on the basis of the Very Persistent (vP) and Very Bioaccumulative (vB) properties highlighted in the risk assessment conducted under the ESR (ECHA, 2008). The chemical was subsequently listed on Annex XIV to the REACH legislation (the Authorisation List) (ECHA, 2014a). Authorisation must be obtained for this chemical to be used in the European Union. No additional work has been completed for musk ketone under the REACH legislation.

United States of America

The chemicals in this group do not belong to any of the chemical classes covered by an Existing Chemical Action Plan and have not been selected for action plan development (US EPA, 2013).

Japan

Musk xylene has been identified as a persistent and highly bioaccumulative chemical, with unclear long-term toxicity to humans and predator animals at higher trophic levels. The chemical has been designated as a Monitoring Chemical Substance under *The Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc.* (NITE, 2014b). Introducers of the chemical must report the volume of the chemical manufactured or imported, and may be required to conduct toxicity testing (Government of Japan, 2010).

The remaining members of this group are identified as existing chemicals and are not subject to use restrictions (NITE, 2014b).

Environmental Exposure

Available international use data indicate that chemicals in this group continue to be used as components of synthetic fragrances, which are incorporated into a wide variety of consumer products, including cosmetics and cleaning products (both household and commercial). The formulations of similar products on the market in Australia are assumed to not differ significantly from those found internationally. Therefore, nitromusk fragrance chemicals are expected to be found in a range of household and commercial products available for use in Australia.

Chemicals used in cosmetics and cleaning products are typically released to sewer as a normal part of their use in domestic and industrial applications. 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 the chemicals in the group, up to approximately 60% of the total volume of these chemicals entering a typical STP may be removed by adsorption to sludge, which may be applied to land as biosolids (Struijs, 1996). Hence, emissions of nitromusks to both environmental surface waters and soils are considered as part of this assessment.

Environmental Fate

Partitioning

The chemicals in this group are expected to remain in soil, or partition to water and sediment, when released from industrial uses.

The chemicals in this group are all neutral organic chemicals that are only slightly soluble in water and slightly volatile (ECB, 2005a; 2005b; LMC, 2013; US EPA, 2008). Estimated Henry's Law constants for the group ($< 3.8 \times 10^{-3}$ Pa-m^3/mol) indicate very slight volatility from water and moist soil (US EPA, 2008). The log K_{ow}values available for the chemicals in this group demonstrate generally high lipophilicity, which suggest limited mobility in soil. This is supported by the estimated soil adsorption coefficients (K_{oc}) for the group (log K_{oc}> 3.4) (US EPA, 2008).

Calculations with a standard multimedia partitioning (fugacity) model assuming equal and continuous distributions to air, water and soil compartments (Level III approach) predict that the chemicals in this group will mainly partition to the soil compartment (approximately 85%), with minor partitioning to the water compartment (approximately 5–10%) and the sediment compartment (approximately 5–10%) (US EPA, 2008). All chemicals in this group are expected to remain in the soil compartment if released solely to soil (US EPA, 2008). However, with sole release to the water compartment, various partitioning patterns are predicted. The more lipophilic musk xylene and musk moskene are predicted to predominantly partition to sediment (approximately 75%), with moderate partitioning to the water compartment (approximately 25%). In contrast, the less lipophilic musk ketone and musk ambrette are predicted to predominantly partition to water (approximately 85%), with minor partitioning to sediment (approximately 15%) (US EPA, 2008).

Degradation

The chemicals in this group are expected to be persistent in the environment. Some data suggest potential for persistent, lipophilic and toxic degradation products to form in the environment.

The chemicals in this group are not expected to undergo rapid ultimate biodegradation in water or soil. Musk xylene has been found to be not readily biodegradable in a study conducted in accordance with OECD Test Guideline (TG) 301C, undergoing 0% degradation in 28 days (ECB, 2005a). Musk ketone has been found to be not inherently biodegradable in a study conducted in accordance with OECD TG 302C, undergoing 0% degradation in 28 days (ECB, 2005b). Musk moskene has been similarly found to be not inherently biodegradable in a study conducted to the same test guideline (OSPAR Commission, 2000). No measured biodegradation data are available for musk ambrette, but rapid ultimate biodegradation is not expected due to the structural similarity of this chemical to the other recalcitrant chemicals in this group.

Available information indicates that musk ketone and musk xylene undergo primary degradation in sewage treatment plants, water, and soil, with degradation involving the reduction of a nitro group to an amine group (ECB, 2005a; 2005b). It is unclear how quickly this reaction occurs. The amine degradation products appear to be persistent in the environment (Gatermann, et al., 1998; Herren and Berset, 2000 ; Osemwengie and Steinberg, 2001; Rimkus, et al., 1999). They are expected to have moderate to high lipophilicity (predicted log K_{ow} = 4.29 and 4.16, respectively) and high toxicity (OSPAR Commission, 2000; US EPA, 2008; 2012). Some data also show potential for these degradation products to bind to the (o)estrogen receptor in *Oncorrhynchus mykiss* (rainbow trout) and the frog *Xenopus laevis* (ECB, 2005a; 2005b), which may indicate potential for endocrine-mediated toxic effects.

No experimental data have been identified for the degradation pathways of musk ambrette or musk moskene in the environment. However, due to the structural similarities of the chemicals in the nitromusk group, primary biodegradation of musk ambrette and musk moskene to stable amine degradation products analogous to those formed from musk ketone and musk xylene is possible.

Although minimal partitioning to the air compartment is expected, it is noted that the chemicals in this group are predicted to undergo relatively slow photo-oxidation by hydroxyl radicals in the troposphere (half life > 6.1 days) (US EPA, 2008).

Bioaccumulation

The chemicals in this group have a moderate to high potential to bioconcentrate in aquatic organisms. Bioconcentration potential is expected to be highest for musk xylene and musk moskene.

Available experimental data demonstrate moderate potential for musk ketone to bioconcentrate, with a study conducted in accordance with OECD TG 305E reporting a bioconcentration factor (BCF) of 1380 L/kg wet weight in *O. mykiss*. The reported bioconcentration factor was based on total radioactivity and includes multiple identified polar metabolites of musk ketone. The study concluded that the BCF for the parent chemical alone would be less than this value and also found evidence of rapid depuration of musk ketone in the form of polar metabolites (ECB, 2005b).

In a study conducted in accordance with OECD TG 305C, the reported BCFs for the more lipophilic musk xylene in the fish *Cyprinus carpio* are 3250 L/kg and 6810 L/kg wet weight. A surfactant was used to disperse the chemical (NITE, 2014a). As discussed in the European risk assessment for musk xylene, additional studies have found musk xylene wet weight BCFs within the same range for other fish species, and a BCF in fish of 4400 L/kg was ultimately selected for the hazard evaluation of this substance in Europe (ECB, 2005a; Rimkus, et al., 1997).

The potential for bioaccumulation of these substances in aquatic organisms based on the results of laboratory tests is supported by environmental monitoring data. Both musk ketone and musk xylene have been identified in fish and shellfish sampled from multiple sites in both fresh and marine waters in Europe and Japan (ECB, 2005a; 2005b).

No evidence has been identified in this assessment to indicate that these chemicals biomagnify through the aquatic food chain. However, the European risk assessments for both substances describe a 2001 study in which the levels of musk ketone and musk xylene in marine fish species sampled in Norway close to municipal sewage treatment plants were highest in the livers of predatory fish (haddock and Atlantic cod), which are towards the top of the marine food chain (ECB, 2005a; 2005b).

No experimental bioaccumulation data are available for musk ambrette and musk moskene. Therefore, K_{ow} values have been used to provide an indication of the bioaccumulation potential of these chemicals. Musk ambrette (predicted log K_{ow} = 4.17) is less lipophilic than musk ketone (log K_{ow} = 4.6). Based on the comparative log K_{ow}values and the measured bioconcentration data available for musk ketone, musk ambrette is expected to have moderate bioaccumulation potential (BCF < 2000 L/kg). Musk moskene (log K_{ow} = 5.3) is more lipophilic than musk xylene (log K_{ow} = 4.9). Based on these comparative log K_{ow}values and the measured bioconcentration data available for musk xylene, musk moskene is expected to have high bioaccumulation potential (BCF ≥ 2000 L/kg).

No data are available to evaluate the potential for the chemicals in this group to bioaccumulate in sediment-dwelling organisms.

Musk ketone and musk xylene have both been identified in human breast milk at concentrations up to 238 µg/kg and 150 µg/kg, respectively (Reiner, et al., 2007). Musk xylene has also been detected in human adipose tissue (Muller, et al., 1996). However, it is noted that humans may experience direct exposure to these chemicals from the use of cosmetic and personal care products, and these findings are therefore not necessarily indicative of transfer of these chemicals through the food chain.

Transport

The chemicals in this group may undergo long-range transport.

Environmental monitoring has identified musk ketone and musk xylene 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 nitromusks to these sites by wet and gaseous deposition after transport of the chemicals through the atmosphere from distant emission sources (Schmid, et al., 2007). This is supported by further studies which have detected nitromusks in rainfall (Peters, et al., 2008), and by their persistence in air. Based on these data, there is potential for the chemicals in this group to undergo long-range transport in the environment.

Predicted Environmental Concentration (PEC)

Predicted environmental concentrations were estimated for the chemicals in this group based on available international monitoring data.

In the absence of reported Australian environmental monitoring data, standard exposure modelling for the release of chemicals to surface waters in STP effluents was used to calculate riverine environmental concentrations of 21.8 µg/L, 23.6 µg/L, 47.9 µg/L, and 23.6 µg/L for musk ketone, musk xylene, musk ambrette and musk moskene, respectively (EPHC, 2009; NICNAS, 2013; Struijs, 1996). However, international monitoring data suggest these values may overestimate environmental levels. Studies conducted in Europe between 1999 and 2001 found musk ketone to be present in STP effluent at a concentration between 0.04 to 0.71 µg/L, and musk xylene between 0.01 to 0.65 µg/L (OSPAR Commission, 2004). Similar concentrations were also detected in Canadian STP effluent (Lee, et al., 2003). An American study from the same time period found lower concentrations of musk ketone and musk xylene in STP effluent, and failed to detect musk ambrette or musk moskene (Osemwengie and Steinberg, 2001). However, this effluent was obtained downstream from a tertiary STP, which are generally more efficient at removing chemicals from effluents than the secondary treatment plants that are typically employed for treatment of domestic waste water in Australia.

In light of these monitoring data, the calculated riverine environmental concentrations were revised. Based on the presented data, and assuming no dilution of effluent upon release (EPHC, 2009), musk ketone, musk xylene and musk moskene are assigned a PEC of 1 µg/L. As modelling predicted the environmental concentration of musk ambrette to be approximately double that of the other chemicals in this group, this chemical is assigned a PEC of 2 µg/L.

All four chemicals in this group have been identified in STP sludge internationally. A Canadian study published in 2003 identified musk ketone and musk xylene in every sample analysed in concentrations up to 364 µg/kg and 422 µg/kg, respectively (Lee, et al., 2003). An additional Canadian study found musk ambrette to be present in raw sludge from an activated sludge STP at concentrations up to 93.2 µg/kg, and musk moskene to be present in raw sludge from an aerobically-based STP at 151 µg/kg in 2004 (Smyth, et al., 2007). Based on these data, and using the standard Australian modelling parameters (EPHC, 2009), soil concentrations between 1 and 3 µg/kg should be expected if biosolids containing these chemicals are applied. Consecutive use of biosolids in one location will result in cumulative soil concentrations of these persistent chemicals (EPHC, 2009).

The degradation products of musk ketone and musk xylene have also been identified in STP effluent and sludge, and environmental waters. Multiple studies have detected the substances in these media, and at up to 63 times the concentration of the parent chemicals (Gatermann, et al., 1998; Herren and Berset, 2000; Osemwengie and Steinberg, 2001; Rimkus, et al., 1999).

Environmental Effects

Effects on Aquatic Life

The chemicals in this group are expected to cause toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

Acute toxicity

The chemicals in this group are only slightly soluble in water, and therefore the reliability of aquatic toxicity data can be difficult to interpret. This is particularly the case for acute studies conducted under static exposure conditions and studies which report nominal 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 limits have been considered as reliable for the purposes of hazard characterisation.

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across three trophic levels for (a) musk ketone, (b) musk xylene and (c) musk ambrette were reported in the European Union Risk Assessment Reports for musk ketone and musk xylene, and the databases included in the OECD QSAR Toolbox (ECB, 2005a; 2005b; LMC, 2013). The calculated ecotoxicity to algae for (d) musk moskene is also reported (US EPA, 2012):

Taxon	Endpoint	Method

Taxon	Endpoint	Method
Fish	(b) 14 d LC50 = 0.4 mg/L	Experimental *Danio rerio* (Zebrafish) OECD TG 204; semi-static Nominal value
Invertebrates	(c) 48 h EC50 = 0.62 mg/L	Experimental *Daphnia magna* (Water flea) Static Behavioural changes observed
Algae	(a) 72 h EC50 = 0.24 mg/L	Experimental *Pseudokirchneriella subcapitata* (Green algae) OECD TG 201; static Measured value Reduced growth rate observed
	(d) 96 h EC50 = 0.066 mg/L	Calculated Polynitrobenzenes SAR

The toxicity values reported above for musk ketone and musk xylene were derived from studies in which co-solvents were used to maintain exposure concentrations of these slightly soluble compounds. It is noted that where efforts are not made to maintain exposure concentrations of these substances there may be no acute toxic effects observed. For example, Schramm *et al.* (1996) reported that musk ketone, musk xylene and musk moskene caused no toxic effects in *Daphnia magna* or the algae *Scenedesmus subspicatus* at their reported limits of solubility (0.46 mg/L, 0.15 mg/L, and 0.046 mg/L, respectively).

Chronic toxicity

The following lowest-observed-effect-concentration (LOEC) and no-observed-effect-concentration (NOEC) values for model organisms across three aquatic trophic levels for (a) musk ketone and (b) musk xylene were reported by Carlsson and Norrgren (2004), or in the European Union Risk Assessment Reports for musk ketone and musk xylene (ECB, 2005a; 2005b):

Taxon	Endpoint	Method

Taxon	Endpoint	Method
Fish	(a) LOEC = 0.1 mg/L (b) LOEC = 0.033 mg/L	Experimental *Danio rerio* (Zebrafish), larvae Decreased survival time observed
Invertebrates	(a) 21 d NOEC = 0.17 mg/L	Experimental *Daphnia magna* (Water flea) OECD TG 202, Part II; semi-static Measured value Reproductive toxicity observed
	(b) 21 d NOEC = 0.056 mg/L	Experimental *Daphnia magna* (Water flea) EEC Ring Test Method (1985) Nominal value Reproductive toxicity observed
Algae	(a) 72 h NOEC = 0.088 mg/L	Experimental *Pseudokirchneriella subcapitata* (Green algae) OECD TG 201; static Measured value Reduced growth rate observed

The potential for the parent members of this group (and their amine metabolites) to cause chronic toxic effects in some organisms through (o)estrogen receptor binding pathways has recently been discussed (Taylor, et al., 2014). However, insufficient data are currently available to evaluate the potential for this to cause adverse outcomes in organisms exposed to these substances in the environment.

Effects on Sediment-Dwelling Life

There are no suitable data available to evaluate the effects of these chemicals on sediment-dwelling organisms.

Effects on Terrestrial Life

Musk ketone can cause toxic effects in terrestrial organisms.

Chronic ecotoxicity values have been obtained for the springtail *Folsomia candida* and the earthworm *Eisenia foetida* exposed to musk ketone in studies conducted according to ISO guidelines. A 28 d NOEC of 100 mg/kg dry weight (dw) soil and 8 week

NOEC of 32 mg/kg dw soil were obtained. Reproductive toxicity was observed in both tests (ECB, 2005b).

Predicted No-Effect Concentration (PNEC)

Musk xylene and musk moskene are expected to be highly bioaccumulative and environmentally persistent chemicals. These hazard characteristics combined have the potential to result in a range of long term effects on organisms exposed to these chemicals which cannot be readily identified through standard toxicity tests. For such chemicals, it is not currently possible to estimate a safe exposure concentration using standard extrapolation methods based on laboratory screening level tests. Predicted no-effect concentrations have therefore not been derived for musk xylene or musk moskene.

Algae were found to be most sensitive to chronic toxic effects of musk ketone. Therefore, the results from the standard 72 h algae toxicity test were used to derive an aquatic PNEC. The PNEC for the chemical is calculated to be 0.88 µg/L, based on the 72 h NOEC of 0.088 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, the chemical has moderate bioaccumulation potential in aquatic organisms.

The only measured toxicity value available for musk ambrette was an acute *Daphnia magna* EC50 value. Therefore, the results from the acute aquatic invertebrate test were used to derive an aquatic PNEC. The PNEC for the chemical is calculated to be 0.62 µg/L, based on the 48 h EC50 of 0.62 mg/L and an assessment factor of 1000. A conservative assessment factor of 1000 was selected as limited ecotoxicity data are available and the chemical is expected to have some potential to bioaccumulate in aquatic organisms.

Insufficient data are available to calculate a PNEC for musk ketone or musk ambrette for the sediment or soil compartments.

Categorisation of Environmental Hazard

The categorisation of the environmental hazards of ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- (musk ketone); benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (musk xylene); benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (musk ambrette); and 1*H*-indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (musk moskene) according to domestic environmental hazard thresholds is presented below (EPHC, 2009; NICNAS, 2013):

Persistence

Persistent (P). Based on the results of biodegradation studies conducted on musk ketone, musk xylene and musk moskene, and the structural similarity of these substances, all chemicals in this group (including musk ambrette) are categorised as Persistent.

Bioaccumulation

Musk xylene and musk moskene

Bioaccumulative (B). Based on measured BCFs greater than 2000 L/kg in multiple fish species for musk xylene and a measured log K_{ow}value significantly greater than 4.2 for musk moskene, both chemicals are categorised as Bioaccumulative.

Musk ketone and musk ambrette

Not Bioaccumulative (Not B). Based on a measured BCF value in fish less than 2000 L/kg for musk ketone and a predicted log K_{ow} value less than 4.2 for musk ambrette, both chemicals are categorised as Not Bioaccumulative.

It should be noted that the available data nevertheless indicate moderate potential for bioaccumulation in aquatic organisms for both musk ketone and musk ambrette.

Toxicity

Toxic (T). Based on the available measured and calculated aquatic toxicity data, which demonstrate acute toxicity values below 1 mg/L (and chronic toxicity below 0.1 mg/L for musk xylene and musk ketone), all chemicals in this group are categorised as Toxic.

Summary

Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (musk xylene); and 1*H*-indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (musk moskene) are categorised as:

- P
- B
- T

Ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- (musk ketone); and benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (musk ambrette) are categorised as:

- P
- Not B
- T

Risk Characterisation

Musk xylene and musk moskene have been identified as PBT substances. It is not currently possible to derive a safe environmental exposure level for such chemicals and it is therefore not appropriate to characterise the environmental risks for these chemicals in terms of a risk quotient.

Due to their persistence, PBT chemicals have the potential to become widely dispersed environmental contaminants. Once in the environment, persistent chemicals that are also highly bioaccumulative pose an increased risk of accumulating in exposed organisms and of causing adverse effects. They may also biomagnify through the food chain resulting in very high internal concentrations, especially in top predators. Importantly, it is difficult or impossible to reverse the adverse effects of PBT chemicals once they have been released to the environment. As a result, these chemicals are considered to be of high concern for the environment.

Persistent Organic Pollutants (POPs) are chemicals that are very persistent, very bioaccumulative, toxic, and have potential to undergo long-range transport. Australia is a signatory to the *Stockholm Convention on Persistent Organic Pollutants* (the Stockholm Convention), which identifies POPs and aims to reduce or eliminate the environmental release of POP substances. It is noted that, based on the data presented here, musk xylene and musk moskene may meet the Annex D screening criteria for POPs under the Stockholm Convention (UNEP, 2001).

Based on the PEC and PNEC values determined above, the following Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for musk ketone and musk ambrette for release into rivers:

Chemical	PEC (µg/L)	PNEC (µg/L)	RQ
Musk ketone	1.0	0.88	1.14

Chemical	PEC (µg/L)	PNEC (µg/L)	RQ
Musk ambrette	2.0	0.62	3.23

An RQ greater than 1 indicates that the chemical may pose an unreasonable risk to the environment, as environmental concentrations may exceed levels that cause harmful effects. Therefore, industrial use of musk ketone and musk ambrette may pose an unreasonable risk to the aquatic environment. Insufficient data are available to characterise the risks posed by the release of these chemicals to the sediment and soil compartments.

In addition to the risks posed by the parent nitromusk chemicals in this group, it is further noted that available information suggests potential for the amine degradation products of these chemicals to be of environmental concern. Based on international environmental monitoring studies, it is possible that the concentrations of these degradation products may significantly exceed the concentrations of the parent chemicals in treated effluent released from sewage treatment plants in Australia. These degradants may therefore contribute to the risks posed by nitromusks to the aquatic environment.

Key Findings

The chemicals in this group are used internationally as fragrance compounds in a wide range of products, including cosmetics and cleaning products. A similar use pattern is assumed in Australia.

This assessment establishes benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (musk xylene) and 1*H*-indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (musk moskene) as PBT substances according to domestic environmental hazard criteria. Therefore, these chemicals are considered to be high concern substances. Similar findings have been made internationally.

The data presented in this assessment also suggest that musk xylene and musk moskene may meet the Annex D screening criteria of the *Stockholm Convention on Persistent Organic Pollutants*. In addition, available data suggests degradation products of musk xylene and musk moskene may have PBT characteristics. One study suggests potential for a degradation product of musk xylene to bind to the (o)estrogen receptor in fish and frog species. These complexities have not been analysed in depth in this assessment.

Ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- (musk ketone) and benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (musk ambrette) do not meet the domestic PBT environmental hazard criteria, and are therefore not identified as PBT substances. However, these chemicals are expected to be persistent in the environment, have moderate bioaccumulation potential, and be toxic to aquatic organisms. Based on the risk quotients calculated for these chemicals, musk ketone and musk ambrette may pose an unreasonable risk to the aquatic environment.

Available data suggest degradation products of musk ketone and musk ambrette may also be persistent in the environment, have moderate bioaccumulation potential, and be toxic to aquatic organisms. In addition, one study suggests potential for a degradation product of musk ketone to bind to the (o)estrogen receptor in fish and frog species. These complexities have not been analysed in depth in this assessment.

Recommendations

It is recommended that all chemicals in this group be considered for assessment of environmental concerns at Tier III level under the IMAP framework. The Tier III environmental risk assessment of these chemicals will focus on outstanding areas of uncertainty in the assessment, including the extent of environmental exposure resulting from industrial use in Australia, toxicity across various organisms, the applicability of the Annex D criteria of the *Stockholm Convention on Persistent Organic Pollutants*, and the risks posed by the degradation products of these substances. Further clarification regarding these uncertainties will allow the exploration of appropriate risk management options.

It is further recommended that the Australian Government Department of the Environment consider including benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (musk xylene) and 1*H*-indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (musk moskene) in monitoring programs for potential Persistent Organic Pollutants that are not currently listed on the *Stockholm Convention on Persistent Organic Pollutants*.

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-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- (musk ketone); benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- (musk xylene); benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro- (musk ambrette); and 1*H*-indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (musk moskene) 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 classification of the acute aquatic hazards posed by the chemicals in this group was performed based on the acute ecotoxicity data presented in this assessment. The classification of musk moskene is based on a calculated acute ecotoxicity value which is appropriate where no experimental data are available. The high acute aquatic toxicity of close structural analogues of musk moskene (such as musk xylene) further justifies a conservative approach when applying an acute aquatic hazard classification to this chemical.

The classification of long-term aquatic hazard for musk ketone and musk xylene was performed using the most stringent outcome method of the GHS for non-rapidly degradable substances.

The classification of long-term aquatic hazard for musk ambrette and musk moskene was performed using the GHS method for substances for which adequate chronic toxicity data are not available, noting the non-rapid degradability of these chemicals and their moderate to high bioaccumulation potential in aquatic organisms (UNECE, 2007).

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