Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

Musk tibetene and a structural analogue

Evaluation statement

22 December 2022

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Musk tibetene and a structural analogue

Chemicals in this evaluation

Name	CAS registry number
Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-	145-39-1
Benzene, 3-(1,1-dimethylethyl)-1,5-dimethyl-2,4-dinitro-	84434-22-0

Reason for the evaluation

Evaluation Selection Analysis indicated a potential environmental risk.

Parameters of evaluation

The chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). These chemicals have been assessed for their risks to the environment according to the following parameters:

- for the industrial uses listed in the 'Summary of Use' section
- release primarily to sewage treatment plants as a result of their industrial uses.

These chemicals have been assessed as a group as they are structurally similar and are expected to be released to the environment from similar use patterns.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

Available information indicates that musk tibetene was used as a fragrance ingredient in a range of consumer products worldwide including:

- laundry and dishwashing products
- cleaning and furniture care products
- air freshener products
- cosmetic and personal care products
- automotive care products.

Although information indicates that the use of musk tibetene as a fragrance ingredient is declining due to international restrictions, there is evidence that the chemical may still be in limited use.

No domestic use or introduction information was identified for 3-(1,1-dimethylethyl)-1,5-dimethyl-2,4-dinitrobenzene (DMMT, the analogue of musk tibetene). This compound appears predominately as an impurity in musk xylene (CAS RN 81-15-2), for which the use does not greatly differ from the use of musk tibetene.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemicals are:

- Persistent (P)
- Bioaccumulative (B)
- Toxic (T).

Musk tibetene and DMMT are closely related to other nitromusk substances and are expected to have similar hazard characteristics. The parent chemicals are persistent and bioaccumulative, with difficult to predict toxicity characteristics. They are expected to partially degrade to amine-containing metabolites, which are expected to be persistent, bioaccumulative and toxic based on a combination of read across and standard quantitative structure activity relationships (QSAR) modelling.

Musk tibetene may have the characteristics of a Persistent Organic Pollutant (POP) under the criteria in paragraph 1 of Annex D of the Stockholm Convention on Persistent Organic Pollutants (the Stockholm Convention).

Environmental hazard classification

The chemicals satisfy the criteria for classification according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) for environmental hazards (UNECE 2017). This evaluation does not consider classification of physical hazards and health hazards.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 4	H413: May cause long lasting harmful effects to aquatic life

Insufficient acute and chronic toxicity data suitable for classification are available to classify the chemicals as they are poorly soluble in water. Therefore, according to the GHS guidance on classification of aquatic hazards (4.1.2.2), the long term aquatic hazards of the chemicals are classified as Category Chronic 4 (i.e., the “safety net” classification) (UNECE 2017).

Summary of environmental risk

Musk tibetene has historical uses as a fragrance ingredient in personal care and other domestic products. DMMT is present as an impurity in products containing other nitromusk fragrances. Based on their historical uses, both chemicals would be expected to be disposed to wastewater and released to the environment through sewage treatment plant (STP) effluents and derived biosolids. The chemicals are expected to undergo biotransformation in anaerobic areas of the STP to amino-metabolites.

Both chemicals are persistent, bioaccumulative and toxic according to domestic PBT criteria. PBT chemicals may become widely dispersed environmental contaminants, with potential for unpredictable adverse effects on environmental organisms. Therefore, PBT chemicals are considered to be highly hazardous to the environment.

The global use of musk tibetene is expected to be low due to regulatory action in a number of jurisdictions and phase outs by industry groups. While there remains some evidence of contemporary use of musk tibetene, there is no evidence of active use of musk tibetene or DMMT in Australia. If information becomes available to indicate that environmental exposure is occurring in Australia from introduction and use of these chemicals, a further evaluation of the risks would be required.

Proposed means for managing risk

Inventory listing

To manage the risks to environment from the introduction and use of the chemicals, the Inventory listings for Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro- (musk tibetene; CAS RN 145-39-1) and Benzene, 3-(1,1-dimethylethyl)-1,5-dimethyl-2,4-dinitro- (DMMT; CAS RN 84434-22-0) should be varied under *Section 86* of *the Industrial Chemicals (IC) Act 2019.*

Term of listing	Details
Specific requirements to provide information to the Executive Director under *Section 101* of the *IC Act*	Obligations to provide information apply. You must tell the Executive Director the volume of introduction, use and end use of the chemical within 20 working days if: • the chemical is being introduced for uses other than research and development

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Given the limited expected introduction and use of the chemicals in Australia, the Executive Director is satisfied that the environmental risks identified in this Evaluation Statement can be managed. This is provided that all requirements are met under environmental, workplace health and safety, and poisons legislation as adopted by the relevant state or territory and the proposed means of managing risks are implemented.

However, these chemicals are persistent, bioaccumulative and toxic (PBT) and as such it is important that the introduction and use of such highly hazardous chemicals in Australia are known so that the risks can be appropriately managed. Therefore, a variation to the term of the listing for these chemicals, to add a specific requirement to provide information, is necessary to manage the risks from introduction of the chemicals (see **Proposed means of managing risk**).

Note: Obligations to report additional information about hazards under *Section 100* of the *IC Act 2019* apply.

Supporting information

Grouping rationale

This evaluation considers the environmental risks associated with the industrial uses of musk tibetene and its analogue, 2 structurally related nitrobenzenes with use in fragrances.

Musk tibetene belongs to a larger group of substances called nitromusks, which were developed as synthetic alternatives to natural musk chemicals. The use of these chemicals is in decline worldwide as many members of the nitromusk group are considered chemicals of concern and their use has been regulated internationally.

The evaluation selection analysis (ESA) of the chemicals in this group indicated a need to assess the scale of use in Australia, as current industrial uses of these chemicals are unknown. The ESA highlighted potential persistence, bioaccumulation and toxicity (PBT) hazard characteristics, which indicate a high concern for the environment.

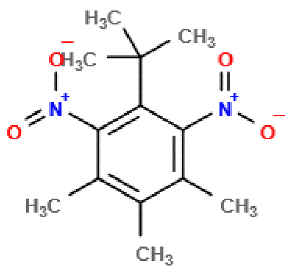
Environmental risks resulting from the use of nitromusk compounds as fragrance ingredients in Australia have previously been assessed under the former Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework established by the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS). An environment Tier II assessment for Nitromusks is available, which determined that 2 of the compounds, musk xylene (CAS RN 81-15-2) and musk moskene (CAS RN 116-66-5), have PBT characteristics (NICNAS 2014).

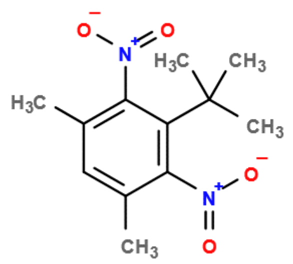
The use of nitromusks such as musk tibetene is declining, and the chemicals are gradually being replaced by other synthetic musks, including macrocyclic musks (RPA 2008). AICIS has conducted risk assessments on ethylene brassylate and exaltone and related macrocylic musks which indicate the use of these replacements present a lower risk to the environment.

Chemical identity

Musk tibetene and its analogue, DMMT, are members of a group of fragrance chemicals known as nitromusks. Nitromusks are a group of structurally related, highly substituted aromatic substances with 2 or 3 nitro groups. Amongst the larger group of nitromusks, the 5 most commercially relevant compounds are the nitrobenzenes musk xylene, musk ketone (CAS RN 81-14-1), musk tibetene and musk ambrette (CAS RN 83-66-9) and the nitroindane derivative musk moskene.

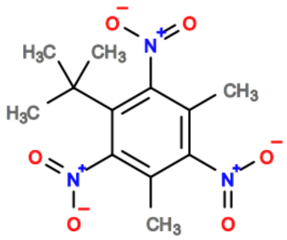
Musk tibetene and DMMT have a common tert-butyl dinitrobenzene structure, with the only difference being that DMMT has one less methyl group. While musk tibetene is prepared through dinitration of the corresponding alkylated benzene precursor, (5-tert-butyl-1,2,3-dimethylbenzene, CAS RN 98-23-7) (Gigante et al. 1995; Opdyke 1975), the analogue only appears to be generated as a by-product in the manufacture of nitromusks such as musk xylene, through incomplete reaction (Suzuki et al. 1999):

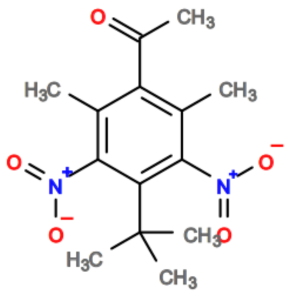
Chemical name	benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-
CAS RN	145-39-1
Synonyms	musk tibetene (MT) 2,6-dinitro-3,4,5-trimethyl-tert-butylbenzene benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro- benzene, 1-tert-butyl-3,4,5-trimethyl-2,6-dinitro
Structural formula	
Molecular formula	$C_{13}H_{18}N_2O_4$
Molecular weight (g/mol)	266.3
SMILES	CC1=C(C)C(=C(C(=C1C)[N+]([O-])=O)C(C)(C)C)[N+]([O-])=O
Chemical description	-

Chemical name	benzene, 3-(1,1-dimethylethyl)-1,5-dimethyl-2,4-dinitro-
CAS RN	84434-22-0
Synonyms	desmethyl musk tibetene (DMMT) 3-(1,1-dimethylethyl)-1,5-dimethyl-2,4-dinitrobenzene 3-tert-butyl-1,5-dimethyl-2,4-dinitro-benzene
Structural formula	
Molecular formula	$C_{12}H_{16}N_2O_4$
Molecular weight (g/mol)	252.27
SMILES	CC1=CC(=C(C(=C1[N+](=O)[O-])C(C)(C)C)[N+](=O)[O-])C
Chemical description	-

Analogue chemicals

The evaluation of musk tibetene and DMMT relies on data from analogue chemicals musk xylene and musk ketone. The chemical identity of these analogues is presented below for structural comparison only; these chemicals are not the subject of this evaluation:

Chemical name	benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro
CAS RN	81-15-2
Synonyms	musk xylene (MX) 1-(1,1-Dimethylethyl)-3,5-dimethyl-2,4,6-trinitrobenzene 5-tert-Butyl-2,4,6-trinitro-m-xylene benzene, 1-tert-butyl-3,5-dimethyl-2,4,6-trinitro 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-]

Chemical name	ethanone, 1-[4-(1,1,-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-
CAS RN	81-14-1
Synonyms	musk ketone (MK) acetophenone, 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitro
Structural formula	
Molecular formula	$C_{12}H_{16}N_2O_4$
Molecular weight (g/mol)	294.3
SMILES	C(C)(=O)c1c(C)c([N+](=O)[O-])c(C(C)(C)C)c([N+](=O)[O-])c1C

Relevant physical and chemical properties

The physical and chemical property data for musk tibetene and DMMT were retrieved from the databases included in the OECD QSAR Toolbox and PubChem, and the Convention for the Protection of the Marine Environment of the North-East Atlantic (the "OSPAR Convention") report on nitromusks (LMC 2020; OSPAR Commission 2004; PubChem 2022). Calculated values were estimated using EPI Suite (US EPA 2017):

Chemical	Musk tibetene	DMMT
Physical form	Solid	Solid
Melting point	135.5 °C (exp.)	128 °C (calc.)
Boiling point	367.5 °C (calc.)	356 °C (calc.)
Vapour pressure	5.22×10^{-4} Pa (calc.)	1.2×10^{-3} Pa (calc.)
Water solubility	0.052 mg/L (exp.)	0.25 mg/L (calc.)
Henry's law constant	0.101 Pa·m^3/mol (calc.)	0.094 Pa·m^3/mol (calc.)
Ionisable in the environment?	No	No
pKa	-	-
log K_{ow}	5.0 (exp.)	4.6 (calc.)

Limited experimental physical and chemical property data are available for musk tibetene or DMMT. Calculations suggest that DMMT will have similar properties to musk tibetene (US EPA 2017).

Musk tibetene and DMMT are slightly volatile and very slightly soluble in water. The high logarithmic octanol-water partition coefficient (log K_{OW}) values indicate that the compounds are highly lipophilic.

Introduction and use

Australia

No specific Australian introduction, use and end use information has been identified.

International

Available information indicates that musk tibetene was used as a fragrance ingredient in a range of consumer products worldwide but use of the chemical is gradually being phased out. DMMT does not appear to have widespread industrial use and is likely to be present as an impurity in formulations containing musk xylene.

Musk tibetene had an estimated annual European use volume of 800 kg in 1995, prior to its subsequent prohibition from use in cosmetic products in the European Union in 2000

(OSPAR Commission 2004). A survey of the Canadian industry in 2000 revealed that there was no declared Canadian use of musk tibetene at volumes 100 kg per annum or greater (Government of Canada 2008a).

The International Fragrance Association (IFRA) prohibits its members from using musk tibetene as fragrance ingredients (IFRA 2022). Some personal care product companies report that they do not use nitromusks in their products (Gleason 2012; Unilever 2022).

Available information indicates that the use of nitromusks as a fragrance ingredient is declining and that this group of chemicals is gradually being replaced by other synthetic musks such as polycyclic and macrocyclic musks (NICNAS 2019).

Musk tibetene is registered as ‘active’ on the US EPA Chemical Substance Inventory, which indicates that it has recently been manufactured, imported or processed by industry in the USA (US EPA 2022).

Historically, nitromusks were used as base notes in fragrance formulations due to their strong scent and fixative properties, whereby they act to bind other fragrance substances to surfaces such as fabrics and skin. Nitromusks were typically used in detergents, fabric softeners and conditioners, cleaning agents, air fresheners and car care products, and cosmetic products (soaps, shampoos and perfumes) (DeLima Associates ; Taylor et al. 2014). Other uses involved are non-industrial applications as additives to fish baits, cigarettes (OSPAR Commission 2004; RPA 2008; SWECO 2010), and food (Daughton and Ternes 1999). Musk tibetene would have non-industrial uses as pesticide (Pang et al. 2006; Ramey et al. 1961) and as an excipient in medicines for topical use only (NICNAS 2019).

Existing Australian regulatory controls

Environment

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

International regulatory status

United Nations

The chemical is not currently identified as a Persistent Organic Pollutant (UNEP 2001), an ozone depleting substance (UNEP 1987), or hazardous substance for the purpose of international trade (UNEP & FAO 1998).

Canada

Musk tibetene was categorised as P, B, and iT (inherently toxic) during the Categorisation of the DSL (OECD 2022). The chemical is listed on the Canadian Domestic Substances List (DSL) and has been subject to CEPA Significant New Activity provisions since 2008 for any activity that involves more than 100 kg per annum (ECCC 2022; Government of Canada 2008b). Musk tibetene is prohibited for use in cosmetic products in Canada (Health Canada 2019).

European Union

Musk tibetene and DMMT are not registered for use under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation (ECHA 2022c).

Musk tibetene is listed in Annex II of the European Union Cosmetic Products Regulation (EC) No 1223/2009 that contains substances which are banned from use in cosmetic products (European Commission 2022). Musk tibetene and DMMT are on the inventory for substances likely to meet the criteria of Annex III to the REACH Regulation, as the 2 chemicals are suspected of being a hazard to the aquatic environment, persistent in the environment, skin sensitisers and toxic for reproduction, and, in the case of musk tibetene, of being a mutagen (ECHA 2022a; ECHA 2022b).

A European Union risk assessment report for the related nitromusk musk xylene concluded that this substance is very persistent and very bioaccumulative (vPvB) and is considered to be borderline T (EC 2011).

Environmental exposure

Nitromusks were historically used as fragrance ingredients internationally and are present in consumer products such as cosmetics, air fresheners, personal hygiene products and various household cleaning agents. Therefore, musk tibetene could potentially be found in consumer and commercial products available for use in Australia.

Chemicals used in cosmetics, personal care and cleaning products are typically released to wastewater as a normal part of their use. Depending on degradation and partitioning processes of chemicals in sewage treatment plants (STPs), some fraction of the quantity of chemicals in wastewater 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 (Struijs 1996). The emissions of the chemicals in this group and their metabolites to environmental surface waters, sediment and soil are considered as part of this evaluation.

Available information indicates that nitromusks are gradually being replaced by macrocyclic and polycyclic musk substances (Lores et al. 2018; Taylor et al. 2014). Despite musk tibetene being prohibited from use in cosmetics in the EU and in Canada, it was recently detected in STP sewage sludge collected during 2017–2019 in the Czech Republic (Košnář et al. 2021). While a 2018 analysis of commercially available cosmetic products in Europe did not detect any of the prohibited nitromusks (Lores et al. 2018), nitromusks may still be used in non-cosmetic formulations such as air fresheners, dishwashing liquids and car care products.

DMMT appears predominately as an impurity in musk xylene (Suzuki et al. 1999). The use patterns of musk xylene do not differ greatly from those of musk tibetene. Therefore, the release patterns and fate of DMMT are expected to be similar to that of musk tibetene.

Nitromusks degrade to highly toxic amine transformation products under anaerobic conditions in STPs. These metabolites are infrequently observed in STP influent but are often detected in sludge and effluent waters, frequently at higher concentrations than the parent nitromusks (Daughton and Ternes 1999; Herren and Berset 2000). Fish in an effluent receiving lake were shown to have large quantities of amine metabolites as compared to parent nitromusks (Osemwengie and Gerstenberger 2004). The metabolites form during STP biotransformation processes or as a result of metabolism in organisms and may be more toxic than the parent compounds (Daughton and Ternes 1999; Herren and Berset 2000).

Therefore, these metabolites must be taken into consideration as an important contributing factor to this evaluation.

Environmental fate

Partitioning

Chemicals in this group are expected to partition to soil, sediment and water when released into the environment.

Musk tibetene and DMMT are neutral organic chemicals that are very slightly soluble in water and slightly volatile. Estimated Henry's Law constants for the 2 chemicals (~ 0.1 Pa·m^3/mol) indicate they will be moderately volatile from water and moist soil. Musk tibetene and its analogue are lipophilic chemicals with high log K_{OW} values (4.6–5) and soil adsorption coefficients (K_{OC} >5 000 L/kg) that indicate they will be immobile in soil and preferentially adsorb to phases in the environment with high organic carbon content (including sediment and soil) (OSPAR Commission 2004; PubChem 2022; US EPA 2017).

Chemicals in this group are expected to be released to the soil and water compartments after treatment at STPs. These chemicals are released to surface waters in STP effluent as a result of not being degraded and released to the soil compartment through application of STP biosolid residues to land. Fugacity calculations (Level III approach) assuming equal release to the water, soil and air compartments (1000 kg/h) predict that the substances will predominately be found in soil (78.6–81.4%), some will partition to water (11–11.7%) and sediment (5.9–9.4%), and negligible quantities to air (0.9–1%) (US EPA 2017).

According to calculations, the amine metabolite of musk tibetene will be slightly more water soluble and less volatile, but with a similar lipophilicity as the parent compound. The K_{OC} value is expected to be lower, indicating increased mobility through soil. This suggests that the metabolite will adsorb to organic matter However it will increasingly be found in the water compartment.

Degradation

Chemicals in this group are expected to be persistent in the environment. They may also degrade to persistent metabolites in the environment.

There are no identified ready biodegradability studies available for musk tibetene or DMMT. *In silico* biodegradation estimates suggest that ultimate degradation of these chemicals will be over a timescale of 10 years (LMC 2015).

The chemicals in this group are expected to be resistant to biodegradation based on the measured half-lives of the closely related compounds, musk xylene and musk ketone. Musk xylene has been found not readily biodegradable in a study conducted in accordance with OECD Test Guideline (TG) 301C, with 0% biological oxygen demand (BOD) after 28 days (ECB 2005b). An inherent biodegradation test with musk ketone following OECD TG 302C gave the same result (0% BOD after 28 days) (ECB 2005a; REACH 2020). Musk tibetene is expected to be similarly resistant to biodegradation.

Similar to related nitromusks, musk tibetene may undergo partial degradation by reduction of a nitro group to an amino group to form an amine-containing metabolite. It is known that microorganisms can reduce nitroaromatic compounds to anilines (Spain 1995). This is likely to occur in anaerobic compartments of STPs, and the corresponding 2- and 4-amino derivatives of musk xylene and musk ketone have been detected in STPs (ECB 2005a; 2005b). Some studies on nitromusks in sewage water and sludge found that where the parent compounds were effectively removed during sewage treatment processes, the levels of amine derivatives often increased (Daughton and Ternes 1999; Herren and Berset 2000). These metabolites are likely to be persistent in the environment (Gatermann Robert et al. 1998; Herren and Berset 2000; Osemwengie and Steinberg 2001; Rimkus et al. 1999).

The chemicals in this group are expected to degrade slowly in the atmosphere through reaction with photogenerated hydroxyl radicals. Calculations performed assuming a typical hydroxyl radical concentration of 1.5 x 10^6 molecules/cm^3 and 12 hours of sunlight per day resulted in a half-life of 7.3 days for musk tibetene (US EPA 2017). An investigation of the photochemical behaviour of musk tibetene found that sunlight and UV irradiation of a suspension of the chemical in water produced 3 indole/indoline derivatives through cyclisation of a nitro and the tert-butyl group to form a cyclic N-oxide. The study found that 13% of the chemical was phototransformed after 200 hours of irradiance with light from a solar simulator (Canterino et al. 2008).

Bioaccumulation

Chemicals in this group and their predicted metabolites are expected to bioaccumulate in aquatic organisms.

Nitromusks, including musk tibetene, are lipophilic compounds with log K_{ow} values of 4.3–5.3 (OSPAR Commission 2004). The log K_{ow} of 5 and 4.6 for musk tibetene and the analogue, respectively, indicates a potential to bioaccumulate in aquatic organisms and both values are above the domestic threshold for categorisation. The expected amine metabolite of musk tibetene has a calculated log K_{ow} of 5.02, indicating a similar potential to bioaccumulate (US EPA 2017).

Bioconcentration factor (BCF) values based on measured data are not available for musk tibetene or DMMT. Calculated values that assume different biotransformation rates are in the range of 133–6624 L/kg for musk tibetene and 259–3966 L/kg for DMMT (US EPA 2017). A BCF for musk tibetene based on wet weight and predicted from the K_{ow} was quoted as 5100–10200 for fish and 1020 for mussels (Beek 1999).

Musk tibetene is likely to demonstrate similar bioaccumulation behaviour to the related chemical musk xylene. Reported measured BCF values for musk xylene are over 5000 L/kg (EC 2011) and 3250 L/kg (rice fish, *Oryzias latipes*, 12 weeks) (NITE 2022). Calculated values for musk xylene give a similar range as that calculated for musk tibetene (133–6624 L/kg) (US EPA 2017).

A Danish study conducted in 1999 found musk tibetene in farmed trout at 13.7 µg/kg fresh weight (Duedahl-Olesen et al. 2005). In studies with other musk compounds, high concentrations of musk substance (largely amine metabolites) in carp tissue relative to lake water were observed and attributed to bioconcentration. It was suggested that the accumulation occurred through exposure to lake sediments or suspended particulate matter (including algae) since carp are bottom feeders (Osemwengie and Gerstenberger 2004).

The bioaccumulation behaviour of nitromusks appears to be species dependent. A study of different species of fish from a STP effluent pond determined bioaccumulation factors normalised to wet weight (BAF_W) of between 290 (rudd fish)–40 000 (eel) for musk xylene and 60 (rudd fish)–1300 (eel) for musk ketone. While significant concentrations of amine metabolites were also found in the fish, no BAF values for these compounds were published (Gatermann R. et al. 2002).

Musk tibetene may biomagnify in food webs, but limited information on this behaviour is available. Musk tibetene was detected in polar bear liver (6 ng/g ww) in Greenland and the Faroe Islands (Vorkamp et al. 2004). Calculations have indicated the potential for the related chemical musk xylene to biomagnify in food webs of air breathing animals (Kelly et al. 2007).

Environmental transport

Chemicals in this group may undergo long-range transport.

Environmental monitoring has identified nitromusks such as musk tibetene and musk xylene in sediment and fish from remote alpine lakes in pristine areas of Switzerland (Bogdal et al. 2009; Schmid et al. 2007). Musk tibetene was detected in polar bear liver in Greenland (Vorkamp et al. 2004). The structurally related chemical musk xylene has been observed in dunlin (*Calidris alpina*) eggs laid in northern Norway after the annual return of these migratory birds from central Europe, suggesting that migratory species may play a role in the long range transport of nitromusks (Mattig et al. 2000).

As the alpine and polar environments do not typically receive direct anthropogenic outputs, the data suggest the potential input of nitromusks to these regions 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 studies which have detected nitromusks in air (Kallenborn et al. 1999) and rainfall (OSPAR Commission 2004; Peters et al. 2008; SWECO 2010), and by the persistence of the chemicals in air.

Predicted environmental concentration (PEC)

Musk tibetene and DMMT have been identified as PBT substances. It is not currently possible to derive a safe environmental exposure level for the chemicals. Therefore, the environmental risks for these chemicals cannot be characterised in terms of a risk quotient (RQ). As such a predicted environmental concentration (PEC) has not been calculated.

Noting that monitoring in surface waters may be difficult due to the chemicals low water solubility (Homem et al. 2015), musk tibetene is typically not found above detection limits or otherwise only in a minority of samples during international monitoring studies. Internationally, the chemical has been measured in STP influent, STP effluent, rainwater, and surface water. Musk tibetene has also been detected in STP sludge and particulates, and in some catchment sediments.

In cases where musk tibetene was quantified in water, concentrations up to 1 ng/L and 0.7 ng/L (STP influent and effluent respectively, Switzerland), 10 ng/L (rainwater) and 640 ng/L (surface water, Switzerland) have been reported (Dimitriou-Christidis et al. 2015; OSPAR Commission 2004; SWECO 2010). In sludge and other particulate matter, musk tibetene was found at concentrations up to 68.9 µg/kg dry weight (dw) in STP sludge samples collected in the Czech Republic (Košnář et al. 2021), and at 67.2 µg/kg dw (mean) in digested biosolids in an earlier Canadian study (Smyth et al. 2007). Another study found 0.42 µg/kg dw of musk tibetene present in sediment of an urban catchment in Singapore (Wang and Kelly 2017).

Environmental effects

Effects on Aquatic Life

Musk tibetene has a very low water solubility. Therefore, the reliability of aquatic toxicity data is unclear. This is particularly the case for acute studies conducted under static exposure conditions and studies which report nominal concentrations of the test substance.

Chemicals in this group are expected to undergo transformation under anaerobic conditions of the STP to form amine degradants that are more water soluble and more toxic to aquatic organisms than parent compounds (Daughton and Ternes 1999). Therefore, in addition to acute toxicity values for parent compounds, calculated values for their metabolites are presented below.

Acute toxicity

The following measured median lethal concentration (LC50) and effective concentration (EC50) values for (a) musk tibetene in model organisms across 3 trophic levels were retrieved from the scientific literature (NITE 2022; Schramm et al. 1996). Calculated values for (a) musk tibetene and (b) DMMT were estimated using EPI Suite (US EPA 2017):

Taxon	Endpoint	Method
Fish	(a) 96 h LC50 ≥0.045 mg/L	Experimental Unreported fish species Nominal value OECD TG 203
	(a) 96 h LC50 = 0.44 mg/L* (b) 96 h LC50 = 0.96 mg/L*	Calculated Neutral Organics SAR
Invertebrate	(a) 48 h EC50 ≥0.052 mg/L	Experimental *Daphnia magna* (water flea) OECD TG 202; Static Nominal Value No effects observed
	(a) 48 h LC50 = 0.33 mg/L* (b) 48 h LC50 = 0.69 mg/L*	Calculated Neutral Organics SAR
Algae	(a) 72 h EC50 ≥0.052 mg/L	Experimental *Scenedesmus subspicatus* (green algae) OECD TG 201; Static Nominal Value No effects observed
	(a) 96h EC50 = 0.78 mg/L* (b) 96h EC50 = 1.39 mg/L*	Calculated Neutral Organics SAR

* Denotes an endpoint greater than the water solubility of the chemical

Available acute ecotoxicity studies of musk tibetene found no toxic effects up to the limit of solubility (0.052 mg/L). No experimental ecotoxicity data were found for DMMT. The estimated endpoints are also greater than the measured and estimated solubility limits of both chemicals.

Since the amine metabolites of nitromusks are more water soluble than the parent compounds and may be highly toxic (Daughton and Ternes 1999) the acute toxicity endpoints for (c) 2-amino musk tibetene and (d) 2-amino DMMT were estimated using EPI Suite and are listed below (US EPA 2017):

Taxon	Endpoint	Method
Fish	(c) 96 h LC50 = 0.37 mg/L (d) 96 h LC50 = 1.09 mg/L	Calculated Neutral Organics SAR
Invertebrate	(c) 48 h LC50 = 0.28 mg/L (d) 48 h LC50 = 0.78 mg/L	Calculated Neutral Organics SAR
Algae	(c) 96 h EC50 = 0.66 mg/L (d) 96 h EC50 = 1.49 mg/L	Calculated Neutral Organics SAR

According to this modelling, 2-Amino musk tibetene and 2-amino-DMMT are similarly or more toxic than the parent compounds at all trophic levels. The estimated toxicity endpoints for both chemicals are consistent with measured values for 4-amino musk xylene, which has reported EC50 values of 0.37–0.51 mg/L for invertebrates (*Daphnia magna*) (ECB 2005b).

Chronic toxicity

There are no chronic toxicity data available for chemicals in this group.

Effects on terrestrial Life

There are no suitable data available to evaluate the effects of these chemicals on terrestrial organisms. Endpoints from related chemicals indicate that they may be slightly toxic to terrestrial invertebrates.

Tests examining toxicity endpoints for earthworms showed that musk xylene causes no changes to survival rate up to the highest test concentration of 50 mg/kg dw (14 day, artificial soil, OECD TG 207). For musk ketone, a 56 d $NOEC_{reproduction}$ of 32 mg/kg dw was observed for earthworms (*Eisenia foetida*, ISO/DIS 11268-2), and a 28 d $NOEC_{reproduction}$ of 100 mg/kg dw for springtails (*Folsomia candida*, ISO/CD 11267 draft 1996) (ECB 2005a; 2005b).

The amine metabolites of nitromusks are more water soluble than the parent compounds and may be highly toxic (Daughton and Ternes 1999) to soil invertebrates as well. Aside from STP effluents and sludge, amine transformation products have also been observed as metabolic products in mammals (Herren and Berset 2000).

Effects on sediment dwelling life

There are no suitable data available to evaluate the effects of musk tibetene and DMMT on sediment-dwelling organisms.

Endocrine effects/activity

The potential for some nitromusks (and their amine metabolites) to cause chronic toxic effects in some organisms through oestrogen receptor binding pathways has been noted in the past (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.

Predicted no-effect concentration (PNEC)

Musk tibetene and DMMT 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 testing. For such chemicals, it is not currently possible to estimate a safe exposure concentration using standard extrapolation methods based on laboratory screening level tests. Therefore, PNECs have not been derived for these substances.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below (EPHC 2009).

Persistence

Persistent (P). Based on estimated degradation data and read across results from chemicals structurally related to musk tibetene, DMMT, and their predicted degradants, musk tibetene and DMMT are categorised as Persistent.

Bioaccumulation

Bioaccumulative (B). Based on calculated bioconcentration factors (BCF) in fish and log K_{ow} values for the chemicals and their predicted degradants, musk tibetene and DMMT are categorised as Bioaccumulative.

Toxicity

Toxic (T). Based on the calculated acute ecotoxicity endpoints below 1 mg/L obtained for the predicted degradants, musk tibetene and DMMT are categorised as Toxic.

Environmental risk characterisation

Musk tibetene and DMMT have been identified as PBT substances. It is not currently possible to derive a safe environmental exposure level for the chemicals. Therefore, the environmental risks for these chemicals cannot be characterised in terms of a risk quotient (RQ).

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.

No current industrial use of musk tibetene and DMMT has been identified in Australia; however, there is evidence of ongoing use in some countries based on their regulatory status and international chemical monitoring.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD 2019) or quantitative adjustments such as assessment factors (OECD 1995). Others must be addressed qualitatively, or on a case by case basis (OECD 2019).

The most consequential areas of uncertainty for this evaluation are:

- No domestic monitoring data are available for musk tibetene and DMMT in surface waters or soil. The risk profile may change should domestic monitoring data become available.
- There is only limited experimental information available for musk tibetene and DMMT. Due to the lack of test data, calculations and read across comparisons with related nitromusks such as musk xylene and musk ketone were necessary. In particular, the lack of chronic toxicity test data is a consequential area of uncertainty. Persistent and bioaccumulative chemicals that are also poorly soluble typically demonstrate adverse effects over long exposure timeframes and low exposure concentrations. The toxic effects of the chemicals in this group may be underestimated in this evaluation, and re-evaluation may be required if new data were to be identified.
- Monitoring studies where low/no concentrations of musk tibetene were observed may not be reliable as the chemicals are difficult to detect using normal HPLC methodologies. A publication suggested that compounds may have low sampling efficiency due to their log K_{ow} value. As a result, low levels of musk tibetene were detected using one HPLC method but not another one (Dimitriou-Christidis et al. 2015). Other factors such as extraction temperature and mode can also cause variations amongst results (Polo et al. 2007). Therefore, environmental distribution of musk tibetene could be wider than indicated in this evaluation.
- Musk tibetene has been prohibited for use in cosmetics in the EU from the year 2000 but was still detected in environmental samples as recently as 2017–2019. Although the rate of detection and concentrations of the substance in samples are relatively low, musk tibetene appears to still be in circulation and contributes to environmental concentrations. There is uncertainty whether this is the result of the use of existing products (from before prohibitions came into effect) or whether products using musk tibetene are currently being manufactured.

References

Beek BE (1999) *Bioaccumulation: New Aspects and Developments*, Springer Nature B.V., Berlin, Germany,

Bogdal C, Schmid P, Zennegg M, Anselmetti FS, Scheringer M and Hungerbühler K (2009) 'Blast from the Past: Melting Glaciers as a Relevant Source for Persistent Organic Pollutants', *Environmental Science & Technology,* **43**(21), pp 8173-8177, doi:10.1021/es901628x.

Canterino M, Marotta R, Temussi F and Zarrelli A (2008) 'Photochemical behaviour of musk tibetene', *Environmental Science and Pollution Research,* **15**(3), pp 182, doi:10.1065/espr2007.12.464.

Daughton CG and Ternes TA (1999) 'Pharmaceuticals and personal care products in the environment: agents of subtle change?', *Environmental health perspectives,* **107**(suppl 6), pp 907-938, doi:doi.org/10.1289/ehp.99107s6907.

DeLima Associates *Consumer Product Information Database,* DeLima Associates website, accessed March 2022.

Dimitriou-Christidis P, Bonvin A, Samanipour S, Hollender J, Rutler R, Westphale J, Gros J and Arey JS (2015) 'GC×GC Quantification of Priority and Emerging Nonpolar Halogenated Micropollutants in All Types of Wastewater Matrices: Analysis Methodology, Chemical Occurrence, and Partitioning', *Environmental Science & Technology,* **49**(13), pp 7914-7925, doi:10.1021/es5049122.

Duedahl-Olesen L, Cederberg T, Pedersen KH and Højgård A (2005) 'Synthetic musk fragrances in trout from Danish fish farms and human milk', *Chemosphere,* **61**(3), pp 422-431, doi:doi.org/10.1016/j.chemosphere.2005.02.004.

EC (2011) *European Union risk assessment report: 5-tert-butyl-2,4,6-trinitro-m-xylene (musk xylene), Addendum to the final report (2005) of the risk assessment*, accessed March 2022.

ECB (2005a) *European Union Risk Assessment Report: 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone (musk ketone),* accessed 27 October 2020.

ECB (2005b) *European Union Risk Assessment Report: 5-tert-butyl-2,4,6-trinitro-m-xylene (musk xylene),* accessed 27 October 2020.

ECCC (2022) *Substances search engine (CAS RN 145-39-1),* Environment and Climate Change Canada (ECCC), accessed February 2022.

ECHA (European Chemicals Agency) (2022a) *Substance Infocard: 5-tert-butyl-4,6-dinitro-m-xylene,* European Chemicals Agency (ECHA), accessed February 2022.

ECHA (European Chemicals Agency) (2022b) *Substance Infocard: 1-tert-butyl-3,4,5-trimethyl-2,6-dinitrobenzene,* European Chemicals Agency (ECHA), accessed February 2022.

ECHA (European Chemicals Agency) (2022c) *Pre-registered substances,* European Chemicals Agency (ECHA), accessed February 2022.

EPHC (Environment Protection and Heritage Council) (2009) *Environmental Risk Assessment Guidance Manual for Industrial Chemicals,* Environment Protection and Heritage Council (EPHC), accessed September 2022.

European Commission (2022) *Regulation (EC) No 1223/2009 of the European Parliament and the Council of 30 November 2009 on cosmetic products (recast)*, European Commission, accessed February 2022.

Gatermann R, Hühnerfuss H, Rimkus G, Attar A and Kettrup A (1998) 'Occurrence of musk xylene and musk ketone metabolites in the aquatic environment', *Chemosphere,* **36**(11), pp 2535-2547, doi:doi.org/10.1016/S0045-6535(97)10208-9.

Gatermann R, Biselli S, Hühnerfuss H, Rimkus GG, Hecker M and Karbe L (2002) 'Synthetic musks in the environment. Part 1: Species-dependent bioaccumulation of polycyclic and nitro musk fragrances in freshwater fish and mussels', *Arch Environ Contam Toxicol,* **42**(4), pp 437-46, doi:10.1007/s00244-001-0041-2.

Gigante B, Prazeres AO, Marcelo-Curto MJ, Cornelis A and Laszlo P (1995) 'Mild and Selective Nitration by Claycop', *The Journal of Organic Chemistry,* **60**(11), pp 3445-3447, doi:10.1021/jo00116a034.

Gleason J (2012) *Nitromusks, Diacetyl Among Materials Phased Out in J&J Fragrance Plan,* Allured Business Media, Carol Stream, Illinois, USA, accessed February 2022.

Government of Canada (2008a) *Final screening assessment report for potentially toxic substances*, Government of Canada, accessed February 2022.

Government of Canada (2008b) *Canada Gazette Part II, Vol. 142, No. 13*, Government of Canada, accessed February 2022.

Health Canada (2019) *Cosmetic Ingredient Hotlist,* Health Canada, accessed February 2022.

Herren D and Berset JD (2000) 'Nitro musks, nitro musk amino metabolites and polycyclic musks in sewage sludges: Quantitative determination by HRGC-ion-trap-MS/MS and mass spectral characterization of the amino metabolites', *Chemosphere,* **40**(5), pp 565-574, doi:doi.org/10.1016/S0045-6535(99)00325-2.

Homem V, Silva JA, Ratola N, Santos L and Alves A (2015) 'Long lasting perfume – A review of synthetic musks in WWTPs', *Journal of Environmental Management,* **149**, pp 168-192, doi:doi.org/10.1016/j.jenvman.2014.10.008.

IFRA (2022) *IFRA Standards,* accessed February 2022.

Kallenborn R, Gatermann R, Planting S, Rimkus GG, Lund M, Schlabach M and Burkow IC (1999) 'Gas chromatographic determination of synthetic musk compounds in Norwegian air samples', *Journal of Chromatography A,* **846**(1), pp 295-306, doi:doi.org/10.1016/S0021-9673(99)00259-9.

Kelly BC, Ikonomou MG, Blair JD, Morin AE and Gobas FAPC (2007) 'Food Web-Specific Biomagnification of Persistent Organic Pollutants', *Science,* **317**(5835), pp 236-239, doi:10.1126/science.1138275.

Košnář Z, Mercl F, Chane AD, Pierdonà L, Míchal P and Tlustoš P (2021) 'Occurrence of synthetic polycyclic and nitro musk compounds in sewage sludge from municipal wastewater treatment plants', *Science of The Total Environment,* **801**, pp 149777, doi:doi.org/10.1016/j.scitotenv.2021.149777.

LMC (2015) *OASIS Catalogic*, v 5.11.17. Laboratory of Mathematical Chemistry (LMC), University "Prof. Dr. Assen Zlatarov".

LMC (2020) *The OECD QSAR Toolbox*, v 4.4.1. Laboratory of Mathematical Chemistry (LMC), University "Prof. Dr. Assen Zlatarov".

Lores M, Celeiro M, Rubio L, Llompart M and Garcia-Jares C (2018) 'Extreme cosmetics and borderline products: an analytical-based survey of European regulation compliance', *Analytical and Bioanalytical Chemistry,* **410**(27), pp 7085-7102, doi:10.1007/s00216-018-1312-3.

Mattig FR, Rösner H-U, Gießing K and Becker PH (2000) 'Umweltchemikalien in Eiern des Alpenstrandläufers (Calidris alpina) aus Nordnorwegen im Vergleich zu Eiern von Brutvogelarten des Wattenmeeres', *Journal für Ornithologie,* **141**(3), pp 361-369, doi:doi.org/10.1046/j.1439-0361.2000.99054.x.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) *Inventory Multi-Tiered Assessment and Prioritisation Framework: Environmental Tier II assessment for 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 1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- (Musk moskene)*

NICNAS (2019) *Inventory Multi-Tiered Assessment and Prioritisation Framework: Human Health Tier III Assessment for the Nitromusks Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-, Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-, 1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- and Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-*, accessed February 2022.

NITE (2022) *Japan Chemicals Collaborative Knowledge Database (J-CHECK),* National Institute of Technology and Evaluation (NITE), accessed February 2022.

OECD (1995) OECD Environment Monographs No. 92, Series on Testing and Assessment No. 3, *Guidance document for aquatic effects assessment*, accessed February 2022.

OECD (2019) *Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment, Series on Testing and Assessment No. 311, Environment, Health and Safety Division, Environment Directorate* The Organisation for Economic Co-operation and Development accessed February 2022.

OECD (2022) *Categorization Results from the Canadian Domestic Substance List,* Organisation for Economic Cooperation and Development (OECD), accessed February 2022.

Opdyke DLJ (1975) 'Musk tibetene', *Food and Cosmetics Toxicology,* **13**(6), pp 879, doi:doi.org/10.1016/0015-6264(75)90262-X.

Osemwengie LI and Steinberg S (2001) 'On-site solid-phase extraction and laboratory analysis of ultra-trace synthetic musks in municipal sewage effluent using gas chromatography–mass spectrometry in the full-scan mode', *Journal of Chromatography A,* **932**(1), pp 107-118, doi:doi.org/10.1016/S0021-9673(01)01216-X.

Osemwengie LI and Gerstenberger SL (2004) 'Levels of synthetic musk compounds in municipal wastewater for potential estimation of biota exposure in receiving waters', *Journal of Environmental Monitoring,* **6**(6), pp 533-539, doi:10.1039/B400514G.

OSPAR Commission (2004) *OSPAR Background Document on Musk Xylene and Other Musks*, Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR Convention) Commission, accessed October 2020.

Pang G-F, Liu Y-M, Fan C-L, Zhang J-J, Cao Y-Z, Li X-M, Li Z-Y, Wu Y-P and Guo T-T (2006) 'Simultaneous determination of 405 pesticide residues in grain by accelerated solvent extraction then gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry', *Analytical and Bioanalytical Chemistry,* **384**(6), pp 1366-1408, doi:10.1007/s00216-005-0237-9.

Peters RJB, Beeltje H and van Delft RJ (2008) 'Xeno-estrogenic compounds in precipitation', *Journal of Environmental Monitoring,* **10**(6), pp 760-769, doi:10.1039/B805983G.

Polo M, Garcia-Jares C, Llompart M and Cela R (2007) 'Optimization of a sensitive method for the determination of nitro musk fragrances in waters by solid-phase microextraction and gas chromatography with micro electron capture detection using factorial experimental design', *Analytical and Bioanalytical Chemistry,* **388**(8), pp 1789-1798, doi:10.1007/s00216-007-1359-z.

PubChem (2022) *PubChem Compound Summary for CID 67350, Musk tibetene,* accessed February 2022.

Ramey D, Hughes W and Van Overbeek J (1961) *Herbicidal Method Employing Dinitropolyalkyl Benzenes*, accessed February 2022.

REACH (2020) *REACH registration dossier for 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone (CAS RN 81-14-1),* Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), accessed February 2022.

Rimkus GG, Gatermann R and Hühnerfuss H (1999) 'Musk xylene and musk ketone amino metabolites in the aquatic environment', *Toxicology Letters,* **111**(1), pp 5-15, doi:doi.org/10.1016/S0378-4274(99)00190-3.

RPA (2008) *Data on Manufacture, Import, Export, Uses and Releases of Musk Xylene (CAS RN 81-15-2) as well as Information on Potential Alternatives to its Use,* Risk and Policy Analysts, London, UK, accessed February 2022.

Schmid P, Kohler M, Gujer E, Zennegg M and Lanfranchi M (2007) 'Persistent organic pollutants, brominated flame retardants and synthetic musks in fish from remote alpine lakes in Switzerland', *Chemosphere,* **67**(9), pp S16-S21, doi:doi.org/10.1016/j.chemosphere.2006.05.080.

Schramm KW, Kaune A, Beck B, Thumm W, Behechti A, Kettrup A and Nickolova P (1996) 'Acute toxicities of five nitromusk compounds in Daphnia, algae and photoluminescent bacteria', *Water Research,* **30**(10), pp 2247-2250, doi:doi.org/10.1016/0043-1354(96)00101-7.

Smyth S, Lishman L, McBean E, Kleywegt S, Yang J, Svoboda M, Lee H and Seto P (2007) International Water Association Journal, *Fate of Polycyclic and Nitro Musks during Aerobic and Anaerobic Sludge Digestion*, accessed February 2022.

Spain JC (1995) 'BIODEGRADATION OF NITROAROMATIC COMPOUNDS', *Annual Review of Microbiology,* **49**(1), pp 523-555, doi:10.1146/annurev.mi.49.100195.002515.

Struijs J (1996) *SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants*, National Institute of Public Health and the Environment, accessed February 2022

Suzuki H, Hisatome K and Nonoyama N (1999) 'Non-acid Synthesis of Nitro Musks Based on the Ozone-Mediated Nitration Using Nitrogen Dioxide', *Synthesis,* **1999**(08), pp 1291-1293, doi:10.1055/s-1999-3544.

SWECO (2010) *Screening of musk substances and metabolites*, accessed February 2022.

Taylor KM, Weisskopf M and Shine J (2014) 'Human exposure to nitro musks and the evaluation of their potential toxicity: an overview', *Environmental Health,* **13**(1), pp 14, doi:10.1186/1476-069X-13-14.

UNECE (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition,* United Nations Economic Commission for Europe (UNECE), accessed March 2022.

UNEP (1987) *The Montreal Protocol on Substances that Deplete the Ozone Layer,* United Nations Environment Programme (UNEP), Ozone Secretariat, accessed February 2022.

UNEP (2001) *The Stockholm Convention on Persistent Organic Pollutants,* United Nations Environment Programme (UNEP) Secretariat of the Stockholm Convention, accessed February 2022.

UNEP & FAO (1998) *Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade,* United Nations Environment Programme (UNEP) and Food and Agriculture Organization (FAO) of the United Nations, accessed February 2022.

Unilever (2022) *Fragrances,* Unilever PLC, London, UK, accessed February 2022.

US EPA (2017) *Estimation Programs Interface (EPI) SuiteTM for Microsoft Windows®*, v 4.11. United States Environmental Protection Agency (US EPA).

US EPA (2022) *TSCA Chemical Substance Inventory,* United States Environmental Protection Agency (US EPA), accessed February 2022.

Vorkamp K, Dam M, Riget F, Fauser P, Bossi R and Hansen AB (2004) *Screening of "new" contaminants in the marine environment of Greenland and the Faroe Islands*, Ministry of the Environment NERI, accessed February 2022.

Wang Q and Kelly BC (2017) 'Occurrence and distribution of synthetic musks, triclosan and methyl triclosan in a tropical urban catchment: Influence of land-use proximity, rainfall and physicochemical properties', *Science of The Total Environment,* **574**, pp 1439-1447, doi:doi.org/10.1016/j.scitotenv.2016.08.091.