Nitromusks: Human health tier II assessment

24 April 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-	81-14-1
Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-	81-15-2
1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-	116-66-5
Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-	145-39-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS

already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are structurally-related, synthetic alkylated nitrobenzene compounds collectively known as nitromusks. These structurally related nitrobenzene compounds are widely used industrially as synthetic musk fragrances in various cosmetic, personal care and domestic products. The major route of exposure in humans is through personal care products and household products. These compounds are retained in human adipose tissue and are excreted in breast milk (Taylor et al., 2014). Similar concerns have been identified internationally, and some regulatory agencies have implemented risk management measures for nitromusks (NICNASa).

Based on these considerations, the chemicals in this group present generally similar human health concerns for cosmetic and domestic use in Australia.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD, 2002a and OECD, 2002b); Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and various international assessments (SCCNFPa, 2004; SCCNFPb, 2004; EU RAR, 2005a; EU RAR, 2005b; OECD 2005 and 2007).

The chemicals have reported use as fragrance ingredients in cosmetic, domestic and commercial products. The concentration of the musk ketone (CAS No. 81-14-1) and musk xylene (CAS No. 81-15-2) in end products is reported to be up to 1 % with typical concentrations of approximately 0.6 % in eau de toilettes, 0.02–0.3 % in other cosmetic products, 0.02 % in detergents and 0.07 % in air fresheners.

The chemicals can also have non-industrial uses as food additives and in pharmaceuticals.

The chemicals, with the exception of musk ketone, are listed as prohibited in the International Fragrance Association (IFRA) Standards (47th amendment) (see **Restrictions: International**) and were not reported by IFRA as being used in fragrance compounds in 2011 (IFRA). The IFRA-affiliated member companies represent approximately 90 % of the world's production volume of fragrances. However, whilst use quantities have been reported to decline over the last 10 years, usage of the chemicals is still reported internationally. Musk ketone and musk xylene were reported to be present in >100 and >60 preparations, respectively, in Nordic countries (SPIN). A Chinese study published in 2011 found musk ketone to be present in over half of the 158 household products tested, with musk xylene detected in one in five of the tested products (Taylor, et al., 2014; NICNASa)

Restrictions

Australian

No known restrictions have been identified.

International

Musk ketone and musk xylene

The chemicals musk ketone (CAS No: 81-14-1), musk xylene (CAS No: 81-15-2) and musk tibetene (CAS No. 145-39-1) are listed on the following (Galleria Chemica):

- EU Regulation (EC) No 1223/2009 Annex III: List of substances which cosmetic ingredients must not contain except subject to the restrictions laid down;
- New Zealand: Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- Association of Southeast Asian Nations (ASEAN): Cosmetic Directive Annex III, part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions.

In the above listed directives, the chemicals are restricted in all cosmetic products, with the exception of oral care products, to the following maximum concentrations:

- 1.4 % for musk ketone and 1.0 % for musk xylene in fine fragrance;
- 0.56 % for musk ketone and 0.4 % for musk xylene in eau de toilette; and

- 0.042 % for musk ketone and 0.03 % for musk xylene in other products.

IFRA Standard (47th amendment) states that 'Musk ketone should only be used if it contains less than 0.1% of musk xylene'.

Musk xylene (CAS No: 81-15-2) is listed in Annex XIV 'The Authorization List' with a sunset date of 21st August 2014 (date from which the placing on the market and the use of a substance is prohibited, unless an authorisation is granted) (ECHA, 2014).

Musk moskene and musk tibetene

Musk moskene (CAS No: 116-66-5) and musk tibetene (CAS No: 145-39-1) are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

These chemicals are prohibited under the IFRA Standard (47th amendment).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals, musk ketone (CAS No: 81-14-1) and musk xylene (CAS No: 81-15-2), are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- R40 Carc. Cat 3 (carcinogenicity)

Musk moskene (CAS No: 116-66-5) and musk tibetene (CAS No: 145-39-1) are not listed on the HSIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Although the chemicals in this group have no reported Australian use data, available international use data indicate use of these chemicals as components of synthetic fragrances, incorporated into a wide variety of consumer products, including cosmetics and cleaning products (in household and commercial products). Therefore, the chemicals in this group are expected to be found in a range of household and commercial products available for use in Australia. An environmental assessment of the chemicals in this group has determined that musk xylene and musk moskene are persistent, bioaccumulative and toxic (PBT) to the

environment. Musk ketone is persistent and toxic, but not bioaccumulative. It is not possible to derive a safe exposure level for such chemicals due to their persistence. These PBT chemicals remain in the enviroment for long periods of time and bioaccumulate in the food chain, building up or accumulating in the body tissues, giving rise to higher overall exposure to these chemicals and increased risk of adverse effects (NICNAS).

Limited information is available on musk moskene (CAS No: 116-66-5) and musk tibetene (CAS No: 145-39-1). These chemicals have been prohibited from use in fragrance products due to the adverse effects from structurally similar compounds (Taylor et al., 2014).

Toxicokinetics

Based on an available toxicokinetics study on oral exposure in rats, the EU RAR (2005b) calculated that approximately 50 % of musk xylene is absorbed using the oral route. There are several toxicokinetics studies on dermal exposure in rats and humans. In rats, after a six-hour dermal application of ^{14}C-labelled musk ketone (CAS No. 81-14-1), 40 % of the applied dose was absorbed within 48 hours while 2–3.5 % remained on the skin. About 7–11 % of the applied dose was excreted in urine and 17–27 % in faeces. Of the metabolites, the highest amounts were excreted during the first 48 hours.

In another study in rats, after a six-hour dermal application of ^{14}C-labelled musk xylene (CAS No. 81-15-2), 20 % of the applied dose was absorbed within 48 hours while 2 % remained on the skin. After 120 hours, 4 % of the applied dose was excreted in urine and 14–15 % in faeces. About 0.2 % of the applied dose remained in the body.

In human studies, when ^{14}C-labelled musk ketone was applied dermally on human skin, it was poorly absorbed over six hours. Only 0.5 % of the applied dose was excreted in urine and faeces within 120 hours and >86 % of the applied dose was recovered from the application site. Therefore, on a conservative basis, it is assumed that 14 % was absorbed (EU RAR, 2005a).

Musk xylene absorption through the human skin (after a six-hour dermal application) was lower than in rat studies, with 90 % of the applied dose as ^{14}C-labelled musk xylene being recovered from the site of application. Only 0.26 % and <0.1 % of the applied dose was excreted in urine and faeces respectively with 120 hours.

Musk ketone is metabolised in rats and humans by glucuronide conjugation (EU RAR, 2005a). Metabolism of musk xylene involves both reduction of a nitro group to an amine group and hydroxylation of methyl groups. The main identified metabolite in bile is hydroxymethyl-musk xylene (EU RAR, 2005b).

Toxicokinetic studies have demonstrated that musk ketone and musk xylene are distributed to nearly all tissues and that the highest levels are found in the gastrointestinal tract, liver, adipose tissue, adrenals, thyroid and kidneys. Both chemicals were found in rat and human milk (EU RAR 2005a & b).

Acute Toxicity

Oral

The chemicals have low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats and mice for musk ketone and musk xylene is >2000 mg/kg bw.

In an animal study, musk ketone (CAS No. 81-14-1) in corn oil was administered by oral gavage to 18 male rats (strain not specified) at doses of 2500, 5000 or 10000 mg/kg bw once (six male rats/dose). Three of the six rats died at the highest dose of 10,000 mg/kg bw with observed effects being bloody discharge around the nose, hyperexcitability, depression, coma and death. No deaths were reported at 2500 and 5000 mg/kg bw (EU RAR, 2005a; HSDB).

In another animal study, musk xylene (CAS No. 81-15-2) suspended in a 0.25 % gum arabic solution was administered to groups of five male and five female mice (strain not specified) by oral gavage at single doses of 125, 250, 500, 1000, 2000 or 4000 mg/kg bw. The observation period was 14 days. Male and female mice at the 4000 mg/kg bw dose showed tremors 3–18

hours after treatment, but no other treatment-related effects were observed. The LD50 in mice is >4000 mg/kg bw (EU RAR, 2005b; HSDB).

Dermal

The chemicals in this group have low acute toxicity based on animal tests following dermal exposure.

In a dermal acute toxicity study, musk ketone (CAS No. 81-14-1) as a 40 % suspension in corn oil was applied once to the clipped rabbit skin to groups of three albino rabbits at doses of 2000 or 10000 mg/kg bw under occlusion for 24 hours. No signs of dermal irritation or systemic toxicity were observed during the seven-day observation period (EU RAR, 2005a; HSDB).

Musk xylene (CAS No. 81-15-2) as a suspension in mazola oil was applied once to the skin of groups of three albino rabbits at 10,000 or 15,000 mg/kg bw for 24 hours under occluded conditions. No signs of irritation or systemic toxicity were observed (EU RAR, 2005b; HSDB).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemicals in this group are not skin irritants.

In a skin irritation study, musk ketone (CAS No. 81-14-1) as a 40 % suspension in corn oil was applied once to rabbit skin for 24 hours under occlusion. No skin irritation was reported (EU RAR, 2005a).

In a non-guideline study, single application of 10,000 or 15,000 mg/kg bw of musk xylene (CAS No. 81-15-2) in mazola oil to the skin of three rabbits did not cause signs of skin irritation and no mortality was observed (EU RAR, 2005b; HSDB).

Eye Irritation

Based on the available data, the chemicals in this group are not eye irritants.

In an eye irritation study according to OECD Test Guideline (TG) 405, 0.1 mL (0.07 g) of musk ketone (CAS No. 81-41) was instilled into one eye of each of six New Zealand White rabbits. Both eyes of three of the rabbits were rinsed 30 seconds post instillation. The eyes of the remaining three rabbits remained unrinsed. No effects were observed on the cornea and iris 72 hours post instillation. In the unrinsed animals, slight to moderate redness and slight swelling of the conjunctivae were observed 1–24 hours after instillation. However, all signs were reversed by 48 hours (EU RAR, 2005a; HSDB).

In an eye irritation study in six New Zealand White rabbits conducted according to OECD TG 405, 0.075 g musk xylene (CAS No. 81-15-2) was instilled in the conjunctival sac of the right eye. Both eyes of three of the rabbits were rinsed 30 seconds after instillation. Observations were made up to 72 hours post-instillation. No effects were observed on the cornea and iris and moderate to slight redness and slight swelling were seen in the conjunctivae of the animals with unrinsed eyes. All signs were reversed at 48 hours observation. Slight redness and swelling were also observed in rinsed animals and these reversed within 24 to 48 hours post instillation (EU RAR, 2005b; HSDB).

Observation in humans

Based on the available information from the EU RAR 2005a, musk xylene (CAS No: 81-15-2) is a slight skin irritant in human volunteers.

In a dermatogical clinic in Copenhagen, 192 patients were patch tested with 0.1 % and 1 % concentrations of musk xylene in petrolatum. The patches were applied to the back and kept in place for two days. Slight reactions were found in the range of irritant or doubtful reactions (EU RAR, 2005b; HSDB).

Sensitisation

Skin Sensitisation

The available animal and human data suggest that the chemicals in this group do not warrant hazard classification for skin sensitisation.

Skin sensitisation studies

In a dermal sensitisation study conducted according to good laboratory practice (GLP) and OECD TG 406, musk ketone (CAS NO. 81-14-1) in a 1:9 acetone/olive oil ratio was applied to 20 female Dunkin-Hartley guinea pigs per group. All animals were induced intradermally with 3 % w/v musk ketone. On day seven, a topical induction application of 75 % w/v musk ketone was used. The chemical challenge dose (7.5, 25 or 75 % w/v) was applied at day 21. At the highest challenge dose, mild redness was seen in 5/20 animals 24 hours after application, but not when checked at 48 hours. While a weak effect was observed (EU RAR, 2005a), this was not considered to meet the classification criteria.

Photoallergy studies

In an animal study, 10 % w/v musk ketone (CAS No. 81-14-1) in acetone was used to treat groups of 10 guinea pigs for four hours/day, three times/week for three consecutive weeks by occluded patch on the clipped and depilated dorsal midline area between the shoulders. The sites were irradiated for two hours with 12 blacklight lamps (ultraviolet A, 320–400 nm) after the patches were removed. Severity of responses was observed at 24 and 48 hours after the challenge. The test groups were challenged with 10 % musk ketone in acetone with a single four-hour occluded patch applied to the site 10–14 days after the induction treatment. The sites were irradiated for two hours after the patch removal and were depilated for 18–20 hours following light exposure to allow scoring. Twenty-four and 48 hours after the challenge, observations were taken to assess the severity of responses. With two positive responses in 10 animals, the chemical was concluded to be weakly photoallergenic (EU RAR, 2005a).

In an photoallergy test, musk xylene (CAS No. 81-15-2) was used at 0.1 mL of 10 % in dimethylacetamide/acetone/ethanol 4:3:3 in groups of 12 female Dunkin-Hartley guinea pigs for 25 minutes on clipped and shaven interscapular skin area of 900 mm^2. All animals were irradiated with 100 kJ/m^2 UV. The procedure was repeated 24 hours later. The animals were challenged 10–14 days after induction with 0.1, 1 or 10 % musk xylene. Observations were made up to 72 hours following application. No sensitisation effects were seen (EU RAR, 2005b; HSDB).

Observation in humans

A range of case reports and human studies suggest that the chemicals in this group are not skin sensitisers.

Musk ketone (CAS No. 81-14-1) was tested for contact sensitisation potential in 25 healthy adult volunteers. Before the exposure testing started, the patch site was treated with a 5 % aqueous sodium lauryl sulfate solution for 24 hours under occlusion. Musk ketone (5 % in petrolatum) was then applied to the forearms for five 3-day cycles consisting of a 48-hour period under occlusion followed by a rest day. A challenge application of musk ketone (5 % in petrolatum) was applied to fresh sites on the back of each volunteer under occlusion for 48 hours following a 10-day rest period. Musk ketone did not produce any sensitisation effects when observed at 48 and 72 hours after application (EU RAR, 2005a).

In a study in 25 volunteers, no sensitisation reaction was seen with musk ketone (CAS No. 81-14-1) applied at 3.2 %. No further details on the study were provided (EU RAR, 2005a, HSDB).

In a study in 100 dermatological patients in Wahlberg, Stockholm, 1 % and 5 % concentrations of musk ketone in petrolatum were patch tested on the back for two days. No responses were observed for either of the concentrations tested (EU RAR, 2005a).

Musk xylene (CAS No. 81-15-2) was tested in a sensitisation test in 25 healthy adult males. Before the exposure testing started, the patch site was treated with a 5 % aqueous sodium lauryl sulfate solution for 24 hours under occlusion. Musk xylene (5 % in petrolatum) was then applied for five 3-day cycles consisting of a 48-hour period under occlusion followed by a rest day. A challenge application of musk xylene (5 % in petrolatum) was applied, under occlusion, to fresh sites on the back of each volunteer for 48 hours following a 10-day rest period. Musk xylene did not cause allergic responses when observed 48 and 72 hours after application (EU RAR, 2005b; HSDB).

In another human study, musk xylene (CAS No. 81-15-2) was patch tested in 100 dermatological patients at concentrations of 0.1 % and 1 % in petrolatum on the back for two days. It was reported that musk xylene did not induce any allergic response (EU RAR, 2005b).

Repeated Dose Toxicity

Oral

With repeated oral exposure to the chemicals in this group, high doses produced histopathological changes in the liver and death. However, the limited available information does not satisfy the criteria for hazard classification.

In an oral repeated dose toxicity study in male B6C3F1 mice, 10 or 200 mg/kg bw/day of musk ketone (CAS No. 81-14-1) dissolved in corn oil was orally administered to the mice for seven days. The relative liver weights increased (14 %) at the highest dose. No treatment-related effects were seen at 10 mg/kg bw/day. No other data were available (EU RAR, 2005a).

In another oral repeated dose toxicity study, male B6C3F1 mice were administered doses of 0, 5, 10, 20, 50, 100, 200 or 500 mg/kg bw/day of musk ketone (CAS No. 81-14-1) in corn oil for seven consecutive days. Dose-related increases in liver weights were observed at doses of 50 mg/kg bw/day up to 500 mg/kg bw/day. Histological changes in the liver included centrilobular hepatocellular hypertrophy and panlobular hepatocellular hypertrophy at the highest dose (EU RAR, 2005a).

In another seven-day study, musk ketone (CAS No. 81-14-1) in corn oil was orally administered to male Fischer 344 (F344) rats at doses of 0, 20, 100, 200 or 500 mg/kg bw/day. A dose-related increase in the absolute liver weights of the rats was seen, with statistical significance at the 100 and 200 mg/kg bw/day doses. A liver weight increase of 42 % more than the controls was seen at the highest dose level. At 500 mg/kg bw/day, rats experienced signs of severe intoxication and death within two days of the start of the study. The administration of 200 mg/kg bw/day was considered the highest tolerated dose (EU RAR, 2005a). No other data were available.

In a 14-day repeated dose toxicity study, eight B6C3F1 mice/sex/dose received a diet containing 0, 0.3, 0.6, 1.25, 2.5 or 5 % of musk xylene (CAS No. 81-15-2) (equivalent to 0, 429, 857, 1786, 3571 or 7143 mg/kg bw/day). Almost all animals at doses ≥857 mg/kg bw/day died after 2–4 days of treatment. Tremors were seen in mice in the higher dose groups. Histological examination of the dead mice showed haemorrhagic erosions in the glandular stomach. No other treatment-related toxic lesions were seen in other organs (EU RAR, 2005b; HSDB).

In a 17-week study, musk xylene (CAS No. 81-15-2) was fed to groups of 10 male and 10 female B6C3F1 mice at doses of 0, 54, 107, 214, 429 or 857 mg/kg bw/day. All animals given 857 mg/kg bw/day dose of musk xylene, and eight males and all females receiving 429 mg/kg bw/day of musk xylene died during the study. No significant treatment-related effects were seen. Histological examination revealed enlargement and irregularity of the liver cells in both sexes at the 214 mg/kg bw/day dose (EU RAR, 2005b).

Dermal

With repeated dermal exposure to the chemicals in this, group liver changes are a concern at high doses. However, the available information does not meet the criteria for hazard classification.

In a 90-day repeated dose toxicity study, groups of 15 Sprague Dawley (SD) rats/sex received dermal applications of 0, 7.5, 24, 75 or 240 mg/kg bw/day of musk ketone (CAS No. 81-14-1) in phenylethyl alcohol. The chemical was applied over approximately 25 % of the clipped surface of the backs of rats under non-occluded conditions. To prevent ingestion, the rats were fitted with collars. No treatment-related deaths or clinical signs were observed. Significant decreases in body weight gains, decreases in red blood cell parameters and increases in absolute (19–20 %) and relative (37–50 %) liver weights were seen at the 240 mg/kg bw/day dose. The study authors did not consider that the haematological parameters, which were within historical controls, to be biologically significant. There were no histopathological changes observed in the liver or other organs. A no observed effect level (NOEL) of 24 mg/kg bw/day was established based on body weight changes at the 75 mg/kg bw/day dose (OECD 2002a; EU RAR, 2005a). Two positive control groups treated with musk ambrette (240 mg/kg bw/day in phenylethyl alcohol), one fitted with a collar and one without, showed clear neurotoxicity and testicular atrophy in rats, regardless of the presence of collars. The positive controls were included, as musk ambrette is known to cause neurotoxicity and testicular atrophy in rats at high dietary and dermal doses (EU RAR, 2005a).

In a 90-day repeated dose dermal toxicity study, groups of 15 SD rats/sex received dermal applications of musk xylene (CAS No. 81-15-2) at 0, 7.5, 24, 75 or 240 mg/kg bw/day in phenylethyl alcohol. The application was applied over approximately 25 % of the clipped surface of the backs of rats under non-occluded conditions. To prevent ingestion the rats were fitted with collars. No treatment-related effects on clinical signs, body weight, haematogical or clinical chemistry parameters were seen. Significant increases in absolute and relative liver weights were seen at the 240 and 75 mg/kg bw/day doses. There were no histopathological changes in the liver or other organs. A NOEL of 24 mg/kg bw/day was established based on liver and body weight changes at 75 mg/kg bw/day (OECD 2002b; EU RAR, 2005b).

Inhalation

The chemicals in this group are not expected to cause serious damage to health by prolonged exposure through inhalation.

In a six-week repeated dose inhalation toxicity study, a group of 20 female Charles River (CD) rats were exposed by whole body inhalation to fragrance mixture A containing 7.2 µg/m^3 of musk ketone (CAS No. 81-14-1) for four hours per day, five days/week for six weeks. Another group of 12 female CD rats and 12 female Syrian golden hamsters were exposed to fragrance mixture D containing 170.5 µg/m^3 of musk ketone for four hours per day, five days per week for 13 weeks. No treatment-related mortality, skin reactions or effects on body weight, behaviour, heamatology and gross pathology or histopathology were observed (EU RAR, 2005a).

Genotoxicity

Based on the available data, the chemicals in this group are not genotoxic. Both in vitro and in vivo assays gave negative results.

In vitro studies

Musk ketone (CAS No. 81-14-1) and musk xylene (CAS No. 81-15-2) have been tested in several in vitro assays, with generally negative results. These included bacterial gene mutation tests, SOS-chromotests, a mammalian gene mutation test, tests for chromosome aberrations and sister-chromatid exchange (SCE) in mammalian cells, a micronucleus test in mammalian cells and an unscheduled DNA synthesis (UDS) test. In all cases, no positive results were observed. Some of the studies are summarised below.

In a bacterial assay, musk ketone (CAS No. 81-14-1) in doses up to 10 mg/plate in dimethyl sulfoxide (DMSO) was tested in five strains of *Salmonella typhimurium*. No mutagenicity was reported with and without metabolic activation (EU RAR, 2005a; HSDB).

In an Ames test, musk xylene (CAS No. 81-15-2) was tested in *S. typhimurium* strains TA 100 and TA 98 with and without metabolic activation up to 500 µg/plate. No treatment-related effects were seen with or without metabolic activation (EU RAR, 2005b).

In a mouse lymphoma mutagenesis assay conducted according to OECD TG 476, musk ketone (CAS No. 81-14-1) in acetone was tested in the L5178Y TK+/- mouse lymphoma cells in the absence (up to dose levels of 4 mg/mL) and presence of S9 (up to

dose levels of 35 μg/mL). No treatment-related positive effects were observed either with or without metabolic activation (EU RAR, 2005a; Taylor et al., 2014).

In an in vitro micronucleus test, musk xylene (CAS NO. 81-15-2) in DMSO was tested in human lymphocytes and in the human hepatoma cell line Hep G2 at doses up to 135 and 350 μM, respectively. The chemical did not increase the frequency of micronuclei in either of the cell lines tested (EU RAR, 2005b).

In vivo studies

In a micronucleus test in male and female ICR mice, all animals received a single intraperitoneal (i.p.) injection with 0, 250, 500 or 1000 mg/kg bw of musk ketone in corn oil. Two out of 20 males and 1/20 females receiving the highest dose died. Clinical signs seen at all dose levels included lethargy and tremors; and diarrhoea at the 1000 mg/kg bw dose. There was no significant increase in the micro-nucleated polychromatic erythrocytes. Slight reduction of up to 28 % in the ratio of polychromatic erythrocytes to normochromatic erythrocytes was observed in all treatment groups (EU RAR, 2005a).

Musk xylene (CAS No. 81-15-2) was administered orally by gavage at three dose levels of 500, 1500 or 5000 mg/kg bw in corn oil to groups of five male F344 rats in an UDS assay. The isolated hepatocytes showed no significant increase in the mean number of net nuclear grain counts (EU RAR, 2005b).

Carcinogenicity

The chemicals, musk ketone (CAS No: 81-14-1) and musk xylene (CAS No: 81-15-2), are classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the HSIS (Safe Work Australia). The available data suggest that the mode of action for musk xylene induction of liver tumours in mice is similar to that for phenobarbital. The relevance of this mode of action to humans has been questioned (EURAR, 2005b). Considering the absence of data on musk moskene and musk tibetene, and the uncertainty regarding the relevance of this mode of action to humans, it is not proposed that any modifications of the classifications for any of the members of the group be recommended.

In a carcinogenicity study, groups of 50 male and 50 female B6C3F1 mice were fed a diet containing 0, 0.075 or 0.15 % musk xylene (equivalent to 0, 70–125 or 141–228 mg/kg bw/day for males and 0, 80–143 or 166–259 mg/kg bw/day for females) for 80 weeks. All animals were maintained on a basal diet without musk xylene after 80 weeks and euthanised in week 90. Microscopic examination of all tissues, including the reproductive organs, was performed. Several organs and tissues in both sexes showed tumour formation. At both doses, musk xylene caused a statistically significant increase in hepatocellular adenomas in both males (0 %: 9/49; 0.075 %: 19/50; 0.15%: 20/47) and females (0 %: 1/46; 0.075 %: 14/50; 0.15 %: 13/49). Males showed a statistically significant increased incidences of hepatocellular carcinomas (0 %: 2/49; 0.075 %: 8/50; 0.15 %: 13/47). A statistically significant increase in harderian gland adenomas was also seen in male animals (EU RAR, 2005a; EU RAR, 2005b).

Investigations into the mechanism behind mouse liver tumours suggest that musk xylene treatment is found to cause a significant induction of liver enzymes such as the cytochromes P450 CYP1A1, 1A2 and 2B and cytochrome b5. Levels of CYP2B in the liver following musk xylene treatment are as high as those caused by phenobarbital (EU RAR, 2005b).

No data are available on the other chemicals in the group.

Reproductive and Developmental Toxicity

There are limited data for fertility effects, and the developmental effects were only observed secondary to maternal toxicity, so the chemicals do not show specific developmental toxicity. The related chemical musk ambrette is considered to have reproductive toxicity and was used as a positive control in one study.

There are no studies that have directly investigated the effects on fertility. However, the 90-day dermal toxicity study with rats and the oral carcinogenicity study in mice did not report adverse effects on the reproductive organs for musk ketone (CAS No. 81-14-1) and musk xylene (CAS No. 81-15-2). This is in contrast to musk ambrette (CAS No. 83-66-9), where testicular atrophy was reported in rats following dermal application for 90 days.

In a developmental toxicity study, eight pregnant SD rats were exposed to 0, 60, 200, 600 or 2,000 mg/kg bw/day musk ketone (CAS No. 81-14-1) in corn oil during gestation days 7–17. The animals were euthanised at day 20 of gestation. Two rats dosed

at 2,000 mg/kg bw/day and three rats dosed at 600 mg/kg bw/day died during the study. At doses of 200 mg/kg bw/day and greater, all animals showed treatment-related clinical signs such as urine-stained abdominal fur, excessive salivation, alopaecia, ungroomed coat, cold to touch, emaciation, red perioral and peri-vaginal substance, chromodacryorrhoea (shedding of bloody tears), chromorhinorrhoea (discharge of a pigmented secretion from the nose) and decrease motor activity. A treatment-related increase in the occurrence of tremors was seen at the 200 mg/kg bw/day dose only at gestation days 7–9. Decreases in foetal body weights, litter sizes and live foetuses, and increases in early and late resorptions and the percentage of resorbed conceptuses occurred at the 200 mg/kg bw/day dose and higher. No other gross foetal alterations were observed (EU RAR, 2005a). Developmental effects were only seen at maternally toxic doses.

In a developmental toxicity study, eight pregnant SD rats were exposed to 0, 60, 200, 600 or 2,000 mg/kg bw/day musk xylene (CAS No. 81-15-2) in corn oil during days 7–17 of gestation. Tremors occurred in all animals. At the 200 mg/kg bw/day dose and greater, all animals showed treatment-related clinical signs such as urine-stained abdominal fur and red perioral substance. Chromodacryorrhoea, dried red or red perioral substance and red substance on forepaws were seen at the 60, 600 and 2,000 mg/kg bw doses. Decreases in foetal body weights, litter sizes and live foetuses, and increases in early and late resorptions and the percentage of resorbed conceptuses occurred at the 200 mg/kg bw/day dose and higher. No other gross foetal alterations were observed (EU RAR, 200ba). Developmental effects were only seen at maternally toxic doses.

In an oral peri/post natal study, 28 time-mated Charles River CD rats received musk xylene (CAS No. 81-15-2) by gavage at doses of 0, 2.5, 7.5 or 25 mg/kg bw/day from day 14 of pregnancy through to weaning on day 21 post partum. The F1 generation was only exposed to the test substance in utero during the peri-natal phase or through any transfer in the milk of the lactating dams. Selected F1 animals were retained to maturity for further testing. Slight and transient reduction in body weight gain was observed at the highest dose of 25 mg/kg bw/day during the first few days of treatment and during lactation. Mean pup weights were slightly lower in this group from day four after birth through to weaning. No effects were seen on the sexual development or fertility in F1 animals. F1 pups euthanised on day 15 or day 22 post partum showed a sex-related difference in the concentrations of musk xylene measured in adipose tissue. Female pups had higher concentrations of musk xylene in fat than in male pups, and concentrations in fat were dose dependent. Higher concentrations in fat were seen at day 15 post partum than at day 22 post postpartum (OECD 2002b; EU RAR 2005b).

Risk Characterisation

Critical Health Effects

The critical health effects for musk xylene and musk ketone for risk characterisation include a systemic long-term effect (carcinogenicity). No critical health effects for musk moskene and musk tibetene have been identified considering the absence of data on carcinogenicity and the uncertainty regarding the relevance of this mode of action to humans.

Public Risk Characterisation

While Australian use information is not available, the chemicals in this group have reported international use as fragrance ingredients in cosmetic and domestic products. The concentration of the musk ketone (CAS No. 81-14-1) and musk xylene (CAS No. 81-15-2) in end products is reported to be up to 1 %, with typical concentrations of approximately 0.6 % in eau de toilettes, 0.02–0.3 % in other cosmetic products, 0.02 % in detergents and 0.07 % in air fresheners (SCCNFPa; SCCNFPb). The literature indicates that musk moskene (CAS No. 116-66-5) has been discontinued from use (Ford et al, 2000).

The EU and ASEAN countries as well as New Zealand have prohibited the use of musk moskene and restricted the use of musk ketone and musk xylene to the low levels identified above (refer **Restrictions: International** section). These chemicals are currently not restricted in Australia for cosmetic and domestic use.

Considering the carcinogenicity data for these chemicals, there is a concern should these chemicals be used in cosmetic and domestic products without any risk management measures. Toxicokinetics studies indicate that up to 14 % of the dermally applied chemicals can be absorbed through human skin. A further concern is that the environmental assessment indicates that musk xylene and musk moskene are persistent, bioaccumulative and toxic to the environment (NICNAS). Musk ketone is persistent and toxic to the environment. Therefore, these considerations should be taken into account when risk managing these chemicals. A quantitative risk assessment at Tier III might help to determine levels at which use of these chemicals are acceptable.

Occupational Risk Characterisation

During product formulation, exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effect, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate for musk ketone and musk xylene.

NICNAS Recommendation

The chemicals are recommended for Tier III assessment to undertake a quantitative risk assessment to further characterise the risk.

Regulatory Control

Work Health and Safety

Musk ketone and musk xylene are recommended for classification and labelling under the current approved criteria and adopted GHS as below. However, musk moskene and musk tibetene are not included in this recommendation. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate,

or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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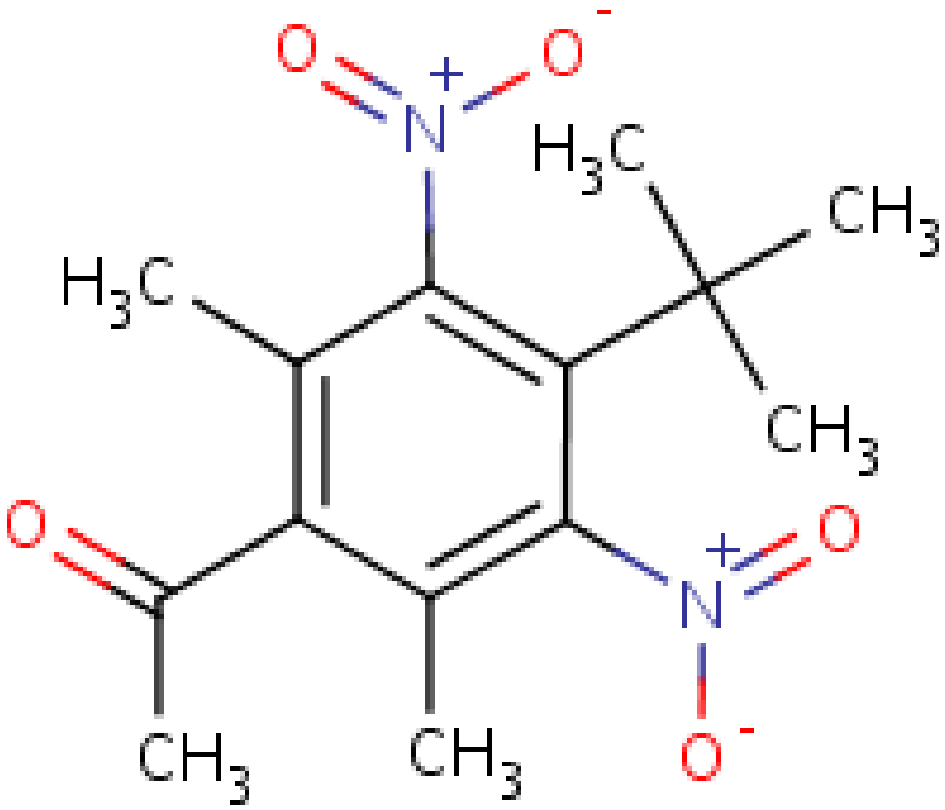
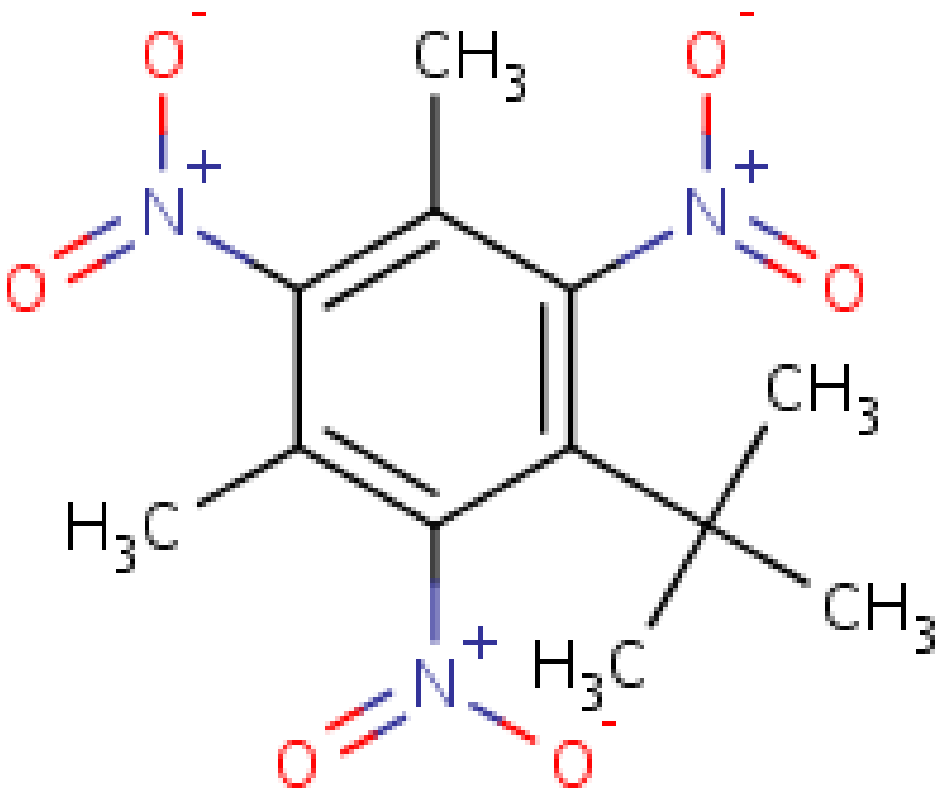
Last Update 24 April 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-** acetophenone, 4-tert-butyl-2,6-dimethyl-3,5-dinitro musk ketone 2,6-dinitro-3,5-dimethyl-4-acetyl-tert-butylbenzene
CAS Number	81-14-1
Structural Formula	

	
Molecular Formula	C14H18N2O5
Molecular Weight	294.30

Chemical Name in the Inventory and Synonyms	**Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-** 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 xylene musk xylol
CAS Number	81-15-2
Structural Formula	



Molecular Formula	C12H15N3O6
Molecular Weight	297.30

Chemical Name in the Inventory and Synonyms	**1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-** lindan, 1,1,3,3,5-pentamethyl-4,6-dinitro moskene musk moskene 4,6-dinitro-1,1,3,3,5-pentamethylindan
CAS Number	116-66-5
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	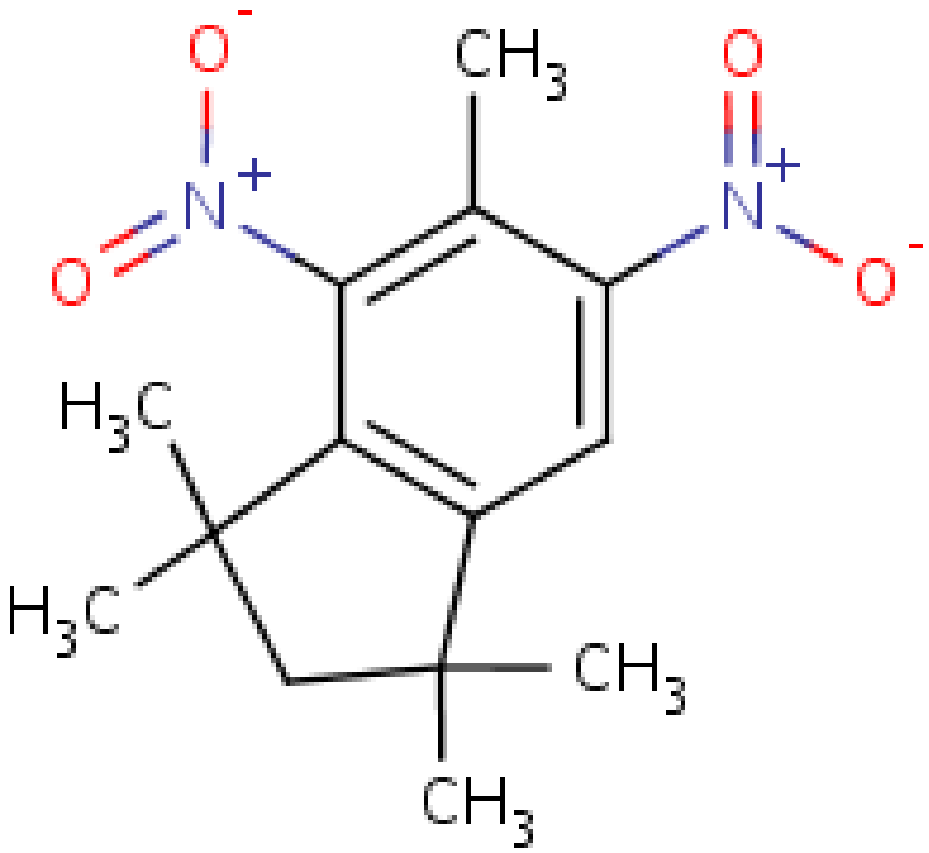
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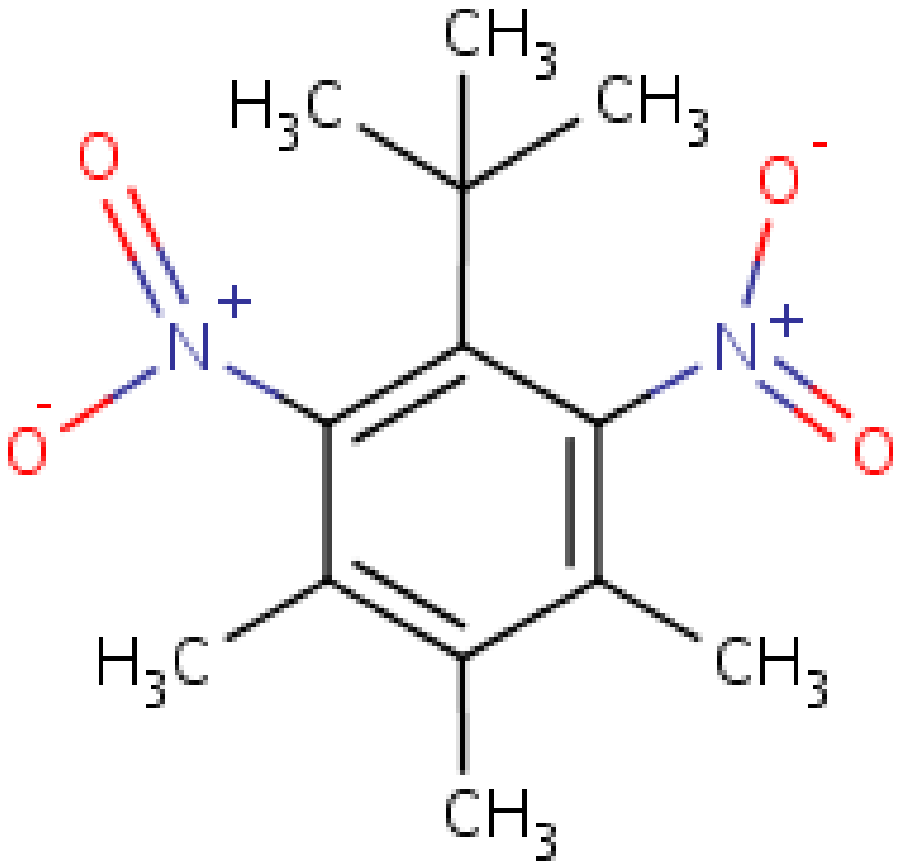
Molecular Weight	278.31

Chemical Name in the Inventory and Synonyms	**Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-** benzene, 1-tert-butyl-3,4,5-trimethyl-2,6-dinitro musk tibetene
CAS Number	145-39-1
Structural Formula	

	
Molecular Formula	C13H18N2O4
Molecular Weight	266.30

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