# Benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro-: Human health tier II assessment

**24 April 2015**

## CAS Number: 83-66-9


- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References


## 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.

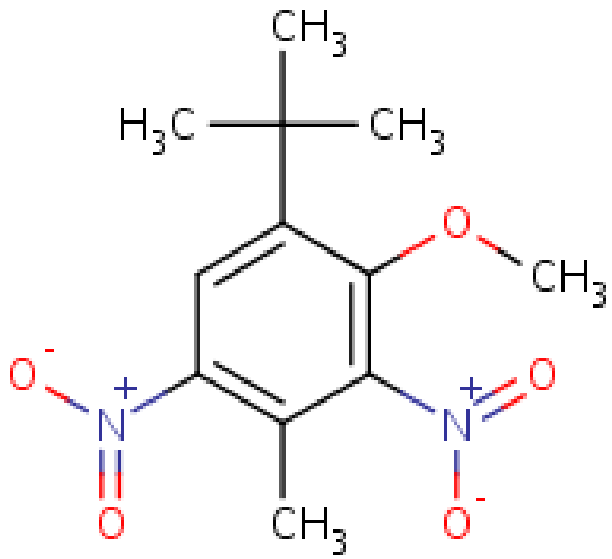
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | 6-tert-butyl-3-methyl-2,4-dinitroanisole<br>anisole, 6-tert-butyl-3-methyl-2,4-dinitro-<br>musk ambrette, artificial<br>amber musk<br>musk ambrette |
| Structural Formula |  |
| Molecular Formula | C12H16N2O5 |
| Molecular Weight (g/mol) | 268.3 |
| Appearance and Odour (where available) | pale yellow powder with musk odour |
| SMILES | C(C)(C)(C)c1c(OC)c(N(=O)=O)c(C)c(N(=O)=O)c1 |

## 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 Galleria Chemica; Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and International Agency for Research on Cancer (IARC) (1996).

The chemical has reported use as a fragrance in cosmetic, domestic and commercial products. The concentration of the chemical in end products is reported to be 0.03–0.2 % in soaps and detergents, 0.01–0.07 % in creams and lotions, and 0.2–2.0 % in perfumes.

The chemical has reported site-limited use in organic synthesis.

The chemical has non-industrial uses including:

- as a flavouring agent in food;
- as an inert ingredient in non-food pesticide products.

## Restrictions

### Australian

No known restrictions have been identified.

### International

The chemical is listed on the following (Galleria Chemica):

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

This chemical is prohibited under the IFRA Standard (47th Amendment).

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

### Exposure Standards

Australian

No specific exposure standards are available.

### International

No specific exposure standards are available.

## Health Hazard Information

Musk ambrette (CAS No. 83-66-9) is structurally related to synthetic alkylated nitrobenzene compounds collectively known as nitromusks. Several nitromusk chemicals have been assessed by NICNAS for both human health and environmental concerns (NICNASa; NICNASb).

Limited information is available on musk ambrette (CAS No. 83-66-9) as this chemical has been prohibited overseas from use in fragrance products due to the adverse neuropathological effects in the brain, spinal cord and peripheral nerves (Spencer et al, 1984; Ford et al, 2000).

### Toxicokinetics

There are no specific toxicokinetics data on musk ambrette (CAS No. 83-66-9). However, based on the available data on musk xylene (CAS No. 81-15-2) and musk ketone (CAS No. 81-14-1), which have similar structural features, it is expected that musk ambrette (CAS No. 83-66-9) will be absorbed via the oral, dermal and inhalation routes of exposure (NICNASa). Nitromusk metabolism in rats and humans is through reduction of the nitro group to an amine group and hydroxylation of methyl groups, followed by glucuronide conjugation.

### Acute Toxicity

#### Oral

The chemical has moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is 339 mg/kg bw (IARC, 1996). No further information is available.

#### Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rabbits is >2000 mg/kg (IARC, 1996). No further information is available.

#### Inhalation

No data are available.

### Corrosion / Irritation

#### Skin Irritation

No data are available on the chemical. However, based on data for musk xylene (CAS No. 81-15-2) and musk ketone (CAS No. 81-14-1), the chemical is not expected to be a skin irritant (NICNASa).

#### Eye Irritation

No data are available on the chemical. However, based on data for musk xylene (CAS No. 81-15-2) and musk ketone (CAS No. 81-14-1), the chemical is not expected to be an eye irritant (NICNASa).

## Sensitisation

### Skin Sensitisation

No animal data are available on the skin sensitisation potential of the chemical.

In a contact and photocontact allergy study, some patients showed contact dermatitis from the chemical (refer **Sensitisation: Observations in humans**). However, the limited data are not sufficiently conclusive to warrant hazard classification for skin sensitisation. The available data suggest that the chemical causes photosensitisation.

***Photoallergy studies***

In a photosensitivity study in guinea pigs, musk ambrette was positive for photosensitivity after application to abraded skin, or under occlusive conditions (Kochever et al, 1979; IARC, 1996). No other details were available.

In a local lymph node assay, musk ambrette did not induce a positive photo-allergic response (Scholes et al, 1991; IARC, 1996). No further details were provided.

### Observation in humans

A range of case reports and human studies suggest that the chemical is a contact sensitiser.

Musk ambrette (CAS No. 83-66-9) was tested for its photosensitisation potential in 495 patients with a standard photo-patch using 5 % musk ambrette in petrolatum and in dimethyl phthalate. Only four cases gave positive results (three men and one woman). The study concluded that a photo-allergic reaction to musk ambrette is a rare event (IARC, 1996; HSDB).

In a study in 19 men, three showed positive photosensitivity to musk ambrette in the photo-patch test (Cronin, 1984; IARC, 1996). No further information was provided.

In a contact and photocontact allergy study, 34 patients using aftershave lotions and other products containing musk ambrette (at concentrations as high as 15 %) were studied. All 34 patients showed facial eczema with the presence of plaques, jawline dermatitis, acute contact dermatitis and chronic actinic dermatitis. The patients' history showed 26 patients were light sensitive and 10 were diagnosed with chronic actinic dermatitis. Seven patients showed pure photocontact dermatitis to musk ambrette as determined by patch and photo-patch tests. Eight patients showed contact allergy to musk ambrette, which was exacerbated by irradiation. Clinical resolution of the clinical signs was seen in most patients who diligently avoided using the products containing musk ambrette (Wojnarowska and Calnan, 1986; IARC, 1996; HSDB).

## Repeated Dose Toxicity

### Oral

Based on the available information, the chemical is neurotoxic via oral exposure. The available data warrant hazard classification (refer **Recommendation** section).

In a repeated dose oral toxicity study in rats (strain not provided), 0.5–4 mg/kg bw/day of musk ambrette was fed to rats in the diet. Treatment-related clinical signs included growth retardation and progressive paralysis of hind limbs at 1.5 mg/kg bw/day. Observations at 16–40 weeks showed complete hind limb paralysis in the animals at the high dose. Depressed erythrocyte counts and haemoglobin values in female rats were observed at doses of ≥1.5 mg/kg bw/day of the chemical. Jaundice at all dose levels was seen (Davies et al, 1967; Spencer et al, 1984). Neuropathological changes reported were primary demyelination and distal axonal degeneration (Ford et al., 1990; IARC, 1996).

In a 12-week repeated dose oral toxicity study, young Sprague Dawley (SD) male and female rats were orally administered musk ambrette at 1500 ppm (approximately 75 mg/kg bw/day) of the chemical. Clinical and haematological examinations were conducted

after six and 12 weeks. Hind limb weakness was observed in 20/40 treated animals (Spencer et al, 1984).

### Dermal

Based on the available information, the chemical is neurotoxic via dermal exposure. The available data warrant hazard classification (refer **Recommendation** section).

In a 12-week repeated dose dermal toxicity study, young SD rats of both sexes were treated by dermal application of a patch with musk ambrette solution in phenyl ethyl alcohol (PEA) at concentrations of 10, 40, 80, or 240 mg/kg bw/day. Clinical and haematological examinations were conducted after six and 12 weeks. No adverse skin reactions to the patch were seen in any of the treatment group. Hind limb weakness was observed in 1/30 animals treated at 40 mg/kg bw/day, 15/30 animals treated at 80 mg/kg bw/day and all animals treated at 240 mg/kg bw/day. All animals treated with 240 mg/kg bw/day showed severe neuropathological changes in the central and peripheral nervous system. The severity of the changes was dose-related (Spencer et al, 1984).

### Inhalation

No data are available.

## Genotoxicity

While there is a concern for genotoxicity, the limited data are not sufficient to warrant hazard classification.

The chemical is mutagenic in *Salmonella typhimurium* (TA100) with metabolic activation by rat liver S9 (IARC, 1996). No further information was provided.

The chemical did not induce micronuclei in the bone marrow of male or female NMRI mice after intraperitoneal injection or after oral dosing. In another study, the chemical induced sex-linked recessive lethal mutations in mature sperm in *Drosophila melanogaster* (IARC, 1996).

## Carcinogenicity

No data are available on the chemical. The data for musk xylene suggest that the mode of action for induction of liver tumours in mice is similar to that for phenobarbital (NICNASa). The relevance of this mode of action to humans has been questioned (EU RAR, 2005a). Considering the absence of data for this chemical, and the uncertainty regarding the relevance of this mode of action to humans, it is not proposed to classify the chemical for carcinogenicity.

## Reproductive and Developmental Toxicity

Based on observed testicular atrophy at low doses there is a concern for reduced fertility. Therefore, the available data warrant hazard classification (refer **Recommendation** section).

In a repeated dose oral toxicity study in rats (strain not provided), 0.5–4 mg/kg bw/day of musk ambrette was fed to rats in the diet. Histopathological investigation showed treatment-related testicular atrophy at 2.5 mg/kg bw/day (Davies et al, 1967; Spencer et al, 1984). For other systemic effects refer to **Repeated dose oral toxicity** section.

In a 12-week repeated dose dermal toxicity study, young SD rats of both sexes were treated by dermal application of a patch with musk ambrette solution in phenyl ethyl alcohol (PEA) at concentrations of 10, 40, 80, or 240 mg/kg bw/day. Clinical and haematological examinations were conducted after six and 12 weeks. Necropsy revealed depressed testicular weight and testicular tubular degeneration in animals receiving 240 mg/kg bw/day (Spencer et al, 1984). For other systemic effects refer to **Repeated dose dermal toxicity** section.

# Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity and neurotoxicity), systemic acute effects (acute toxicity from oral exposure) and local effects (photosensitisation).

### Public Risk Characterisation

While Australian use information is not available, the chemical has reported use as a fragrance ingredient in cosmetic and domestic products. The concentration of musk ambrette (CAS No. 83-66-9) in end products is reported to be up to 2 % with typical concentrations of approximately 0.03–0.2 % in soaps and detergents, 0.01–0.07 % in creams and lotions, and 0.2–2.0 % in perfumes. Literature indicate that musk ambrette (CAS No. 83-66-9) has been prohibited from use in fragrant products due to the adverse neuropathological effects (Spencer et al, 1984; Ford et al, 2000).

EU and ASEAN countries as well as New Zealand have prohibited the use of musk ambrette (refer **Restrictions: International** section). This chemical is currently not restricted in Australia for cosmetic or domestic use.

Considering the neurotoxicity observed at low doses, there is a concern for the use of this chemical in cosmetic and domestic products without any risk management measures.

### Occupational Risk Characterisation

During use and product formulation exposure can 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 chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term and systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposures are implemented. The chemical 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.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section.

## NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetic and domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

### Regulatory Control

#### Public Health

The use of the chemical should be prohibited in cosmetic and domestic products by listing in the *Poisons Standard* (SUSMP, 2015). This is based on neurotoxicity at low concentration, testicular atrophy and potential for photosensitisation.

#### Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Harmful if swallowed (Xn; R22) | Harmful if swallowed - Cat. 4 (H302) |
| Repeat Dose Toxicity | Toxic: Danger of serious damage to health by prolonged exposure in contact with skin and if swallowed (T; R48/24/25) | Causes damage to organs through prolonged or repeated exposure through the dermal and oral routes - Cat. 1 (H372) |
| Reproductive and Developmental Toxicity | Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62) | Suspected of damaging fertility - Cat. 2 (H361f) |

[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 industry

***Control measures***

Control measures to minimise the risk from oral and dermal exposure to the chemical 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 chemical is 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 chemical, 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 chemical.

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 chemical 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 the chemical has not been undertaken as part of this assessment.

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