Benzene, 1-methoxy-4-(1-propenyl)-, (E)-: Human health tier II assessment

21 April 2016

CAS Number: 4180-23-8

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.

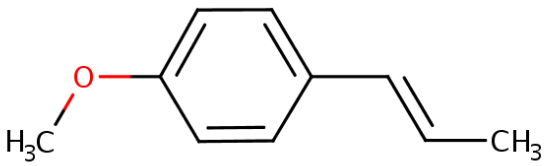
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	anethol, trans- anisole, p-propenyl-, (E)- (E)-1-p-methoxyphenylpropene trans-anethole
Structural Formula	
Molecular Formula	C10H12O
Molecular Weight (g/mol)	148.20
Appearance and Odour (where available)	Clear liquid, sweet odour
SMILES	c1(C={t}CC)ccc(OC)cc1

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;
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the International Fragrance Association (IFRA) transparency list (IFRA, 2011);
- the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR);
- the US National Library of Medicine's Toxicology Data Network (ToxNet);
- the US Food and Drug Administration (FDA) (2013); and
- various international assessments (Joint FAO/WHO Expert Comitee on Food Additives (JECFA) (1991; 1999); the European Food Safety Authority (EFSA) Scientific Opinion on the food safety of allylhydroxybenzenes (EFSA, 2011); and the safety evaluation of generally recognized as safe (GRAS) chemicals by Expert Panel of the Flavour and Extract Manufacturers' Association (FEMA) (Newberne et al., 1999)).

The chemical has reported cosmetic uses in perfumes and fragrances. The Good Scents Company has recommended its use in concentrations up to 10 %.

The chemical has reported domestic uses, including in:

- polishes and waxes;
- soap and cleaning products; and
- air care products.

The chemical has reported commercial use in plastics.

The chemical has reported site-limited use, including in the production of paper and paper products.

The chemical has reported non-industrial uses, including:

- as a food flavouring agent;
- in biocides; and
- in pesticides.

Restrictions

Australian

No known restrictions have been identified.

International

The WHO and EFSA established an acceptable daily intake (ADI) of 2 mg/kg bw.

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

The chemical has an exposure standard of 2 mg/m^3 time weighted average (TWA). (Galleria).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 3-24 mg/m^3 TWA in different countries such as Canada (Alberta, Quebec), France, Iceland, Indonesia, Ireland, Spain, USA (California, Tennessee, Washington), Chile, Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical has been found in human and animal studies to be rapidly absorbed, metabolised and excreted in the urine. It undergoes two metabolic pathways, ?-oxidation and o-demethylation, to yield 4-methoxycinnamyl alcohol (4 MCA) and 4-hydroxy-propenylbenzene (4 OHPB), respectively.

In several human studies, 81 % of the radiolabelled chemical was found to be excreted unchanged in the urine; it was also exhaled as CO_2. The chemical was metabolised by ?-oxidation (major pathway) and o-demethylation (minor pathway) to produce 4 MCA and 4 OHPB, respectively, at doses of 0.05-12 mg/kg body weight (bw)/day. The epoxide metabolite was seen at larger doses (Newberne et al., 1999).

In another study, humans (n=5) were orally administered the chemical at doses of 1, 50 or 250 mg. The major route of elimination was in the urine and via respiration (as CO_2), within 24 h. The primary metabolite was identified as 4-methoxyhippuric acid (a metabolite of 4 MCA), affected by dose (REACH).

In a study conducted on Sprague Dawley (SD) rats (4/dose) and CD-1 mice (4 animals/dose), the chemical was orally administered in the diet at concentrations of 0.1, 0.25, 0.5 or 1 % (rat) or 0.05, 0.1, 0.25 or 0.5 % (mouse), followed by a single dose of [^{14}C side chain 1] trans-anethole. Faeces and urine samples were collected after four days. Tests indicated that the chemical was completely absorbed, metabolised and excreted (WHO, 1999).

In another study, the chemical was repeatedly administered to SD rats, intraperitoneally (I.P.), at a dose of 300 mg/kg bw/day for seven days. Analysis of liver content showed that the chemical induced increases in liver weight, microsomal protein content

and microsomal cytochrome P 450 (WHO, 1999).

The chemical was tested for hepatic microsomal enzyme activity in SD rats (seven females/dose). The animals received doses of 0, 75 or 300 mg/kg bw/day over four days. Homogenates were prepared from the liver and assayed for activity of the microsomal enzymes. There was no effect on liver weight but the study concluded that the chemical induces cytochrome P450 in females (WHO, 1999).

In a study conducted in Wistar rats (three males/dose), the chemical was administered by gavage at doses of 125 and 250 mg/kg bw, once a day for ten days. Results showed that there was an increase in liver weight and phase two enzyme activity at the 250 mg/kg bw dose (Newberne et al., 1999).

A study was conducted in F344/DuCrj rat hepatocytes to determine the metabolites of trans-anethole. Biotransformation of concentrations ranging from 0.25 mM - 1.0 mM over time was studied by high performance liquid chromotography (HPLC) elution profiles. At 0.5 mM, the levels of the two metabolites; 4 OHPB and 4 MCA increased with time. After a 90 minute incubation period, 4 OHPB showed significant activity in the hepatocytes. A dose-dependent cell death, reduction in ATP and reduction in adenine nucleotides were observed (Nakagawa & Suzuki, 2003).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The reported median lethal dose (LD50) values in rats, mice, and guinea pigs were >2000 mg/kg bw.

The LD50 values from oral administration studies in Osborne-Mendel rats and CD-1 mice ranged from 2090-3200, and 1820-5000 mg/kg bw, respectively. Limited reporting of these studies suggested effects including mild liver changes such as slight discolouration, mottling and blunting of lobe edges (WHO, 1991; Newberne et al., 1999).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rabbits was reported as >4900 mg/kg bw.

New Zealand White (NZW) rabbits (6/sex/dose) were applied the chemical semiocclusively at a single dose of 4900 mg/kg bw. No mortality and no overt signs of toxicity were observed up to the 14-day observation period. The LD50 was > 4900 mg/kg bw (REACH).

Inhalation

The chemical has low acute toxicity in animal tests following inhalation exposure.

In a study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 403, Wistar rats (5/sex/dose) were exposed to the chemical by nose-only inhalation for 4 hours at a concentration of 5.1 mg/L. Laboured and noisy breathing, sneezing, decreased activity, hunched posture and poor co-ordination were observed on days following the exposure. All effects were fully reversed after six days. No mortalities were reported (REACH).

Corrosion / Irritation

Skin Irritation

Based on the available information, the chemical is not irritating to the skin.

In a study conducted in accordance with OECD TG 404, the chemical (0.5 mL) was semiocclusively applied to clipped, intact dorsal skin of female NZW rabbits (three animals) for 4 hours. The chemical produced only slight erythema that fully resolved within 8 days (REACH).

Eye Irritation

Based on the available information, the chemical is not irritating to the eye.

In a study conducted according to OECD TG 405, 0.1 mL of the neat chemical was instilled into the eyes of female NZW rabbits (three animals). The animals were observed 1, 24, 48 and 72 hours after treatment. There were no signs of pain or eye irritation (REACH).

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results seen in a guinea pig maximisation test (GPMT) and a local lymph node assay (LLNA). The available information meets the criteria for hazard classification.

In a mouse local lymph node assay (LLNA) conducted according to OECD TG 442B, female CBA mice (four animals/dose) were exposed to concentrations of 25, 50, or 100 % of the chemical in acetone/olive oil (4:1 v/v). The stimulation indices (SI) calculated were 3.49, 3.53 and 3.85 for the low, mid and high doses, respectively. The chemical was positive for skin sensitisation (REACH).

In a GPMT conducted according to the OECD TG 406, ten guinea pigs were induced with the chemical at 2 % (intradermal) and 50 % (topical). The chemical at 10 % was administered as a challenge dose and 10/10 animals tested positive for skin sensitisation. Each guinea pig was then challenged weekly, at a non-irritating concentration and 10/10 guinea pigs tested positive for skin sensitisation (Barrat & Basketier, 1992; REACH).

Repeated Dose Toxicity

Oral

Repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a study conducted similarly to OECD TG 408, the chemical was administered to SD rats (20/sex/dose) in the diet daily for 90 days at doses of 0, 150, 300, 600 and 900 mg/kg bw/day. Effects included reduced food consumption and decreased body weight gain, which were attributed to reduced palatability of the diet. Increased liver weight to body weight ratio was seen in males at 900 mg/kg bw/day. In females, increases in mean values of gamma glutamyltransferase, alanine aminotransferase and aspartate aminotransferase, and decreases in mean values of total protein, albumin and glucose were observed at 600 and 900 mg/kg bw/day. A no observed adverse effect level (NOAEL) of 300 mg/kg bw/day was established for this study (REACH).

In a study conducted similarly to OECD TG 453, SD rats (groups of 52/sex/dose) were orally administered the chemical at 0, 0.25, 0.5 or 1 % for 117 weeks (equivalent to 0, 2500, 5000 or 10000 mg/kg bw/day). A significant decrease in mortality was reported in males in the high dose group and an increase in the relative liver weights was observed in females of all treatment groups. Histopathological investigation of the liver showed the following: non-neoplastic lesions in males and females at the 0.5 and 1 % dose groups, hepatocytic vacuolation, sinusoidal dilation, focal/nodular hyperplasia and hepatocellular hypertrophy (REACH).

In another study, SD rats (52 /dose/sex) were fed the chemical at doses of 0, 0.2, 0.5, 1, or 2 % concentrations for 12-22 months. Transient retardation of body weight gain, anorexia and lethargy were reported in several animals (WHO, 1991; Newberne et al., 1999).

In two studies conducted according to OECD TG 452, Osborne-Mendel rats (10/sex) were fed the chemical at 2500 mg/kg bw for a duration of one year or 10 000 mg/kg bw for a duration of 15 weeks. No treatment-related effects were reported in the one year study. The only effect seen, in males in the 15-week study, was slight hydropic changes of hepatic cells in the liver (Newberne et al., 1999; WHO, 1999; REACH).

CD-1 mice (5/sex/dose) were administered the chemical in the diet at doses of 0, 60, 120, 240, 360 or 500 mg/kg bw/day for 28 days. Mortality was observed in 2/5, 3/5 and 2/5 males at 240, 360 and 500 mg/kg bw/day, respectively, and in 2/5 females at 500 mg/kg bw/day. Reduction in body weight and food consumption was observed in all treatment groups. Significant treatment-related decreases in total leukocyte count were reported in males at 360 mg/kg bw/day and 500 mg/kg bw/day. A NOAEL of 120 mg/kg bw/day was reported (WHO, 1999).

In another study in CD-1 mice (20/sex/group), the animals were given the chemical in the diet at doses of 30, 60, 120 or 240 mg/kg bw/day for 90 days. Mortality and weight changes were seen at doses ≥60 mg/kg bw/day. At doses ≥120 mg/kg bw/day, daily food consumption decreased and the efficiency of food uptake was decreased in males during weeks 3 and 4. Reduction in liver glycogen content and reduced organ (liver, brain, kidney) weights were observed in all doses (Newberne et al., 1999).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the results from the available in vitro and in vivo genotoxicity studies, the chemical is not considered genotoxic.

In vitro studies

The chemical gave negative results in the following tests:

- bacterial reverse mutation assays in *Salmonella typhimurium* (S. typhimurium) strains TA98, TA1538. TA1535, TA1537, TA97, TA98 and TA100 with and without metabolic activation at doses up to 0.10 mg/plate (WHO, 1991; TOXNET);
- mammalian chromosome aberration test (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at doses up to 0.1 mg/plate (REACH); and
- DNA damage and repair, unscheduled DNA synthesis (UDS) (OECD TG 482) in rat hepatocytes tested negative (WHO, 1991).

In vivo studies

The chemical gave negative results in a mouse bone marrow micronucleus test in Swiss mice (4/sex) administered the chemical at doses of 40-400 mg/kg bw by i.p. injection (Abraham, 2001).

Carcinogenicity

Based on the available information, the chemical is not carcinogenic.

In a study conducted similarly to OECD TG 453, SD rats (groups of 52 animals/sex/dose) were orally administered the chemical in the diet at 0, 0.25, 0.5 or 1 %, daily, for 117 weeks (equivalent to 0, 2500, 5000 or 10000 mg/kg bw/day). Increased incidences of benign hepatocellular adenomas and hepatocellular carcinomas in females in the 1 % dose group were reported (Attia et al., 1989; WHO, 1991; REACH).

In another study, SD rats (52 animals/dose/sex) were fed the chemical in diet at 0, 0.2, 0.5, 1, or 2 % concentrations for 12-22 months. Transient retardation of body weight gain, anorexia and lethargy were reported in several animals. The chemical was reported to be non-carcinogenic (WHO, 1991; Newberne et al., 1999).

Several oral administration studies were conducted on A/He and CD-1 mice at doses 148 – 740 mg/kg bw/day. There was no increase in tumour incidence and survival of the groups was reduced to approximately 70 % by the end of the study (Newberne et al., 1999).

Reproductive and Developmental Toxicity

Based on the available information, the chemical does not show specific reproductive or developmental toxicity. Developmental effects were only observed secondary to maternal toxicity.

Female Crl:CD BR rats (10/dose) were administered the chemical by gavage at doses of 0, 25, 175 or 350 mg/kg bw/day for 7 days prior to mating until the fourth day of lactation. During gestation and lactation, decreases in body weight gain and food consumption were observed in the 175 and 350 mg/kg bw/day dose groups. The rats treated with the high dose (350 mg/kg bw/day) had increased mortality rates for the pups; however, no physical abnormalities were seen (Newberne et al., 1999).

In a four-generation study, Wistar rats (20/sex/dose) were administered the chemical in the diet at concentrations of 0 or 1 % (equivalent to 600-1500 mg/kg bw/day). Decreased body weight gain and delayed growth of pups were seen. Decreased food consumption and body weight gain of the dams (generation not specified) were reported in all treated groups, and were attributed to low palatability of the diet containing the chemical. No effects on reproductive parameters were observed over four generations (Newberne et al., 1999; WHO, 1999; REACH).

In another study, SD-derived rats (ten females) were dosed with 0, 35, 175 or 350 mg/kg bw/day in corn oil by gavage for seven days prior to mating, during the seven-day mating period, gestation, and up to the fourth day of lactation. The females were mated with untreated males. At 350 mg/kg bw/day, there were significant reductions in mean body weight and food consumption. Also at this dose, there was a significant decrease in the number of live born pups as well as an increase in mortality rates of the born pups, however; no abnormalities were reported. The chemical did not cause any developmental effects in the rat foetus at doses below those causing maternal toxicity (WHO, 1999).

The chemical was studied for effects on fertility in albino Charles Foster rats (number not specified) with reported dose levels of 50 mg, 70 mg and 80 mg/kg. Females were caged with males of known fertility and doses were administered to pregnant rats orally for 10 days. Dose-dependent effects on implantation were observed, with no implantation seen at the largest dose. A significant increase in mean uterine weight was also observed at the high dose (Dhar, 1995).

Other Health Effects

Endocrine Disruption

A study was conducted in vitro in isolated rat hepatocytes and cultured MCF-7 human breast cancer cells. The chemical was administered at doses varying from 0.25-2 mM. Concentration and time-dependent cell death was observed. An increase in oestrogenic activity at lower concentrations was seen (Nakagawa & Suzuki, 2003).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the local effects of skin sensitisation.

Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemical is reported to be used in cosmetic/domestic products overseas. Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products. In the absence of any regulatory controls, the characterised critical health effect of skin sensitisation has the potential to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

Given the critical local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure 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 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 cosmetics and/or 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

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in domestic and cosmetic products. Due to the toxicity profile at the concentrations reported to be potentially in use, this chemical should be considered for listing in the SUSMP, for labelling as a skin sensitiser, consistent with the *Scheduling Policy Framework* guidelines. Exemptions to scheduling may be applicable at low concentrations.

Matters to be taken into consideration include:

- the known uses of the chemical; although there is no information to confirm that the chemical is currently used in cosmetic and domestic products in Australia, it is reported to be used in cosmetic and domestic products overseas; and
- internationally there is a recommendation for use in concentrations up to 10 %, however, the available data does not preclude skin sensitisation occurring following exposure to concentrations below 10 %.

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]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal and inhalation 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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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