# Benzene, (1-methylethyl)-: Human health tier II assessment

**25 November 2016**

## CAS Number: 98-82-8



## 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.

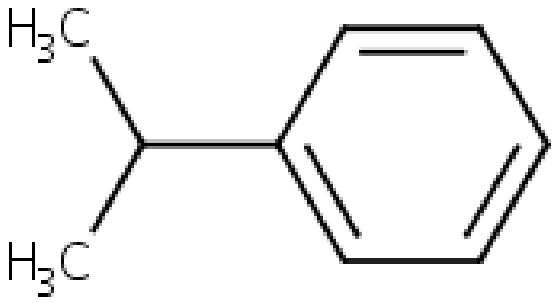
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

**Disclaimer**

Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | isopropylbenzene<br>cumene<br>2-phenylpropane<br>cumol<br>isopropylbenzol |
| Structural Formula |  |
| Molecular Formula | C9H12 |
| Molecular Weight (g/mol) | 120.19 |
| Appearance and Odour (where available) | Colourless liquid, gasoline-like odour |
| SMILES | c1(C(C)C)ccccc1 |

## Import, Manufacture and Use

### Australian

The chemical has reported commercial use in industrial surface coatings.

### 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 Profile (OECD SIAP); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the OECD High Production Volume chemical program (OECD HPV), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Library of Medicine Household Products Database and the International Agency for Research on Carcinogens (IARC).

The chemical has reported domestic uses, including:

- in aerosol propellants;

- in adhesives and binding agents;
- in cleaning and washing products, including fuel system cleaners, concrete cleaners and degreasers;
- in colouring agents;
- in fillers;
- as thinners in paints, lacquers and varnishes;
- in surface treatments such as asphalt primers, masonry water proofers, primer sealers and polyurethane sealers; and
- in surface-active agents.

The chemical has reported commercial uses, including:

- in construction materials;
- in corrosion inhibitors;
- in flame retardants and extinguishing agents;
- in fixing agents;
- in fuel additives in gasoline blends and high-octane aviation fuel;
- in lubricants and additives;
- in insulating materials;
- in photochemicals;
- in impregnation materials;
- in process regulators;
- in reprographic agents;
- as a solvent for fats and resins; and
- in welding and soldering agents.

The chemical has reported site-limited uses, including:

- in manufacturing of styrene, α-methylstyrene, acetophenone, detergents, di-isopropylbenzene;
- in manufacturing rubber, iron, steel, pulp and paper;
- as an intermediate in producing phenol and acetone; and
- as a catalyst in producing acrylic and polyester-type resins.

Non-industrial uses have been identified internationally, including use in pesticides and preservatives.

## Restrictions

### Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 5 (SUSMP, 2016).

Schedule 5:

‘HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), **except**:

a) toluene and xylene when included in Schedule 6;

b) benzene and liquid aromatic hydrocarbons when included in Schedule 7;

c) food grade and pharmaceutical grade white mineral oil;

d) in solid or semi-solid preparations;

e) in preparations containing 25 per cent or less of designated solvents;

f) in preparations packed in pressurised spray packs;

g) in adhesives packed in containers each containing 50 grams or less of adhesive;

h) in writing correction fluids and thinners for writing correction fluids packed in

containers having a capacity of 20 mL or less; or

i) in other preparations when packed in containers with a capacity of 2 mL or less.'

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.'

Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2016).

### International

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

- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles—limits for finished articles (0.01 mg/kg for hydrocarbons, aromatic, non-substituted);
- US FDA Indirect Food Additives: Adhesives and Components of Coatings - Substances for Use Only as Components of Adhesives - Adhesives;
- Switzerland Ordinance of the Federal Department of Home Affairs (FDHA) on articles and materials—Annex 6, List of binders (monomers), Part B: non-evaluated substances; and
- Switzerland Ordinance of the Federal Department of Home Affairs (FDHA) on articles and materials—Annex 6, List of solvents, Part B: non-evaluated substances.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R65 (acute toxicity)
- Xi; R37 (irritation)

### Exposure Standards

#### Australian

The chemical has an exposure standard of 125 mg/m$^3$ (25 ppm) time weighted average (TWA) and 375 mg/m$^3$ (75 ppm) short-term exposure limit (STEL).

#### International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 50–246 mg/m$^3$ (10–50 ppm) time weighted average (TWA) and 250–375 mg/m$^3$ (50–75 ppm) short-term exposure limit (STEL) in different countries such as Europe (Denmark, France, England, Spain), Canada, Mexico and the USA.

## Health Hazard Information

## Toxicokinetics

Metabolism, disposition, and pharmacokinetic studies of the chemical (known as cumene) in rats following oral, intravenous injection, or nose-only inhalation administration have demonstrated that the chemical is well absorbed. Following absorption, a small quantity (approximately 5 %) of the cumene is exhaled unchanged, but the major portion is oxidised at the benzylic carbon to 2-phenyl-2-propanol, with subsequent oxidation to 2-hydroxy-2-phenylpropanoic acid, 2-phenyl-1,2-propanediol, and phenyllactic acid. A minor pathway is oxidation of a methyl group to 2-phenyl-1-propanol and subsequently to 2-phenylpropanoic acid and 2-phenylmalonic acid. A minor metabolite may be phenylmalonic acid. These metabolites are excreted mainly in the urine in conjugated form. Oxidation occurs in both hepatic and extrahepatic tissues, including the lung. Cumene does not bioaccumulate in tissues (NTP, 2009). Isopropenylbenzene (α–methylstyrene) is also a major metabolite of cumene, and has been identified, together with its derivatives, in the exhaled air and urine of rats and mice exposed to cumene (IARC, 2013).

## Acute Toxicity

### Oral

The chemical has low acute oral toxicity based on data available from six rat studies. The reported values for the median lethal dose (LD50) in rats are generally >2000 mg/kg bw. One study with limited details reported an LD50 of 1400 mg/kg bw. Observed sub-lethal effects included central nervous system depression, haemorrhagic lungs, liver discolouration and acute gastrointestinal inflammation (EU RAR, 2001, REACH).

### Dermal

The chemical has low acute dermal toxicity based on data available from three rabbit studies. The median lethal dose (LD50) in rabbits is >3160 mg/kg bw. Signs of toxicity included weight loss, increasing weakness and collapse. Gross autopsy showed haemorrhagic areas of the lungs, liver discolouration, darkened kidneys and spleen and gastrointestinal inflammation (EU RAR, 2001).

The chemical was applied undiluted to New Zealand White (NZW) rabbits (one male or female animal/dose) as single doses at 2000, 3160, 5010, and 7940 mg/kg bw for 24 hours. The animals were observed for 14 days. The LD50 was >3160 mg/kg bw (REACH).

### Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful: may cause lung damage if swallowed’ (Xn; R65) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). This is supported by the low viscosity of cumene as well as the post-mortem examination in an acute oral toxicity assay which identified pulmonary oedema and haemorrhaging had occurred (EU RAR, 2001).

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

No mortalities were observed after six Sprague Dawley (SD) male rats were exposed to the chemical for six hours at 17.6 mg/L. Exposure at 40 mg/L caused deaths in 2/3 rats after four hours exposure. A median lethal concentration (LC50) value in rats >17.6 mg/L was established. The principal causes of death in acutely exposed animals were 'respiratory paralysis, pulmonary oedema and haemorrhaging, lung haemorrhage being associated with further haemorrhage in the thymus, bladder and adrenals. Liver hypertrophy was also described as resulting from compensation for metabolic stress caused by the compound, as were observed splenic deformities' (EU RAR, 2001).

Mice (strain unspecified, 16 animals/sex/dose) were exposed to cumene (nose only) for seven hours at six concentrations between 7 and 12 mg/L. An LC50 value of 2000 ppm (10 mg/L) was determined. Death was caused by respiratory failure due to central nervous system depression (REACH; EU RAR, 2001).

Increased activity and gait abnormalities have been observed in rats at 500 and 1200 ppm (2.5 and 6 mg/L) but not at 100 ppm (0.5 mg/L) in a behavioural study following six hours' exposure to cumene (EU RAR, 2001).

### Observation in humans

When cumene was used as a solvent involving human exposures over a period of one to two years, 'it was found that no toxic injury resulted from daily exposures to those concentrations of vapour that could be readily tolerated. For most persons, the vapours became painful to the eyes and upper respiratory passages in the concentration range of 300 to 400 ppm although some persons readily tolerated concentrations considerably in excess of 400 ppm' (EU RAR, 2001).

## Corrosion / Irritation

### Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37). The available data support this classification.

Cumene is mildly irritating to the respiratory system based on animal studies. The information available from studies in mice indicates that cumene vapour produces irritation in the upper respiratory tract, depressing the respiratory rate by 50 % in the range of 2058–2490 ppm (EU RAR, 2001).

### Skin Irritation

The chemical is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification.

In a study similar to OECD Test Guideline (TG) 404, cumene was applied to the intact and abraded skin of six albino rabbits. The patch sites were observed after 24 and 72 hours. No oedema was observed. Mild reversible erythema was observed in all the rabbits. Average scores (maximum score 8) were 2, 1.5, 2, 2, 2 and 1.5. There was no difference between scores for intact and abraded skin in any of the rabbits (REACH).

### Eye Irritation

The chemical is slightly irritating in rabbit eyes.

In a study similar to OECD TG 405 conducted using a different scoring system, the chemical (0.1 mL) was applied to the eyes of six albino rabbits for 24 hours and the eyes were examined at 24, 48 and 72 hours. The authors reported that the chemical is not irritating (REACH).

In a similar study, the chemical (0.1 mL) was applied to the eyes of six NZW rabbits for 24 hours and the eyes were examined at 24, 48 and 72 hours. The following observations were made after the application: slight discharge and copious discharge (10 minutes), moderate erythema (one hour), moderate erythema and copious discharge containing whitish exudate (14 hour), followed by gradual improvement after 48–72 hours. Effects were fully reversible in all animals 120 hours after application REACH).

### Observation in humans

Cumene is an eye, skin, and mucous membrane irritant. Prolonged contact with liquid cumene may cause erythema or blisters (NTP, 2009).

The limited information regarding humans indicates that cumene vapour concentrations greater than about 400 ppm become very painful to the eyes and upper respiratory passages. Experiences in handling and using cumene has shown a slight risk of dermatitis (EU RAR, 2001).

## Sensitisation

### Skin Sensitisation

Based on the available data, the chemical is not a skin sensitiser.

In a guinea pig maximisation test (GPMT) similar to OECD TG 406 using 20 female guinea pigs (strain unspecified), cumene was not found to be sensitising. After intradermal induction using 10 % cumene solution (maize oil) and topical induction using a 75 % solution (maize oil), a challenge dose of a 40 % test solution (maize oil) was applied to the animals. No responses indicative of skin sensitisation were observed (REACH).

## Repeated Dose Toxicity

### Oral

The chemical does not cause severe toxic effects following repeated oral administration.

In a repeated dose dietary toxicity study, male albino rats (10/dose and one control) were exposed to cumene for 28 days at 250, 2500 and 6000 ppm (approximately equivalent to 22.8, 224.8 and 535.8 mg/kg bw per day). The only significant finding was increased relative testes weight at the mid dose. Survival, food consumption, other organ weights and terminal body weights were not affected by the treatment. The no observed effect level (NOEL) was established as >535.8 mg/kg bw per day (REACH).

In an oral repeated dose toxicity study, cumene was administered five days per week by gavage to rats (female, strain unspecified, 10/dose, 20 controls) for six months at 0, 154, 462 and 769 mg/kg bw/day. Haematology parameters were evaluated at several intervals, including total erythrocytes and leukocytes, haemoglobin content and differential blood cell count. Other evaluations included body weights, food consumption, observations of appearance and behaviour, mortality, macroscopic and microscopic evaluation and organ weights for the lungs, heart, liver, kidneys, spleen and testes. Microscopic examination was also made of the adrenal glands, pancreas, and femoral bone marrow. Slight and moderate increases of average kidney weights were observed at mid and high doses respectively. There were no effects on the haematopoietic system and no histopathological findings following examination of the lungs, heart, liver, kidneys, spleen, testes, adrenal glands, femoral bone marrow or pancreas. A no observed adverse effect

level (NOAEL) of 154 mg/kg bw/day and a lowest observed adverse effect level (LOAEL) of 462 mg/kg bw/day were established based on increases in average kidney weights (EU RAR, 2001; REACH; NTP 2009).

### Dermal

The chemical does not cause severe toxic effects following repeated dermal application.

Diluted cumene (10–20 applications) was applied in unspecified amounts to the skin of white rabbits (species and number of animals unspecified) for two to four weeks. The animals were observed daily and weighed weekly. There was no indication that cumene was absorbed through the skin in toxic amounts based on the gross appearance, behaviour and body weights of the animals during treatment. The repeated application caused moderate irritation (definite erythema) and the development of a thin layer of devitalized tissue, which resulted in exfoliation (EU RAR, 2001).

In an unpublished study, a mixture containing 30 % cumene was applied (2 mL/kg bw/day) to the backs of New Zealand White rabbits for 28 days, with topical application areas no less than 10 % of the total surface area of the rabbits. No systemic toxicological effects were observed either during the experiment or at necropsy. The test animals exhibited skin oedema, fissuring and moderate to severe erythema. Macroscopic and microscopic investigation revealed dermatitis and other cellular dermal effects (EU RAR, 2001).

### Inhalation

Based on the treatment-related effects reported from repeated dose toxicity studies in rats and mice, repeated inhalation exposure to the chemical is not considered to cause serious damage to health except at high concentrations.

In a study conducted in accordance with OECD TG 413, B6C3F1 mice (10/sex/dose) were exposed (whole body) to vapour of the chemical at concentrations of 0, 62.5, 125, 250, 500, and 1000 ppm (equivalent to 0, 11.9, 23.8, 47.5, 95 and 190 mg/m$^3$) for six hours plus T90 (the time taken to reach 90 % of the target concentration within the exposure chamber; 12 minutes) per day, five days per week for 14 weeks. Eight females exposed to 1000 ppm died during week one of the study, Mean body weights of males exposed to 500 or 1000 ppm were significantly less than those of the chamber controls. The eight female mice exposed to 1000 ppm that died during the first week of the study exhibited clinical signs of acute toxicity, including lethargy or ataxia. Liver weights of mice exposed to 500 or 1000 ppm were significantly increased. Weights of the cauda epididymis and spermatid count were significantly decreased in males exposed to 1000 ppm. Final body weight and body weight gain were significantly reduced in males at ≥250 ppm. Absolute kidney weights in males were significantly increased at ≥250 ppm. A no observed adverse effect concentration (NOAEC) of 125 ppm was established in males (NTP 2009; REACH).

In a study conducted in accordance with OECD TG 413, Fischer 344 rats (10/sex/dose for the main study) were exposed (whole body) to vapour of the chemical at concentrations of 0, 62.5, 125, 250, 500, and 1000 ppm (equivalent to 0, 11.9, 23.8, 47.5, 95 and 190 mg/m$^3$) for six hours plus T90 (12 minutes) per day, five days per week for 14 weeks. Additional clinical pathology groups of ten males and ten females were exposed to the same concentrations for 23 days. All rats survived to the end of the study. Mean body weights of all exposed groups were similar to those of the chamber controls. Kidney and liver weights of males exposed to ≥250 ppm and liver weights of females exposed to 1,000 ppm were significantly greater than those of the chamber controls. There were significant differences between females exposed to ≥250 ppm and chamber control females in the relative length of time spent in the oestrous stages. The amount of α2u-globulin in the right kidneys was significantly increased in male rats exposed to 125 ppm or greater. The incidence of medullary granular casts in males exposed ≥250 ppm or greater was significantly increased. The severity of renal tubule cortex hyaline droplet accumulation and regeneration increased with increasing exposure concentration in male rats. A NOAEC was established at 125 ppm based on the effects observed in haematology, clinical chemistry and organ weights. The lowest observed effect concentration (LOEC) was 250 ppm, based on changes in organ weights, incidence of medullary granular casts and time spent in the oestrous stage (NTP, 2009; REACH). The kidney effects seen in male rats are not considered relevant to humans.

In a study conducted in accordance with OECD TG 412, Fischer 344 rats (5/sex/dose for the main study) were exposed (whole body) to vapour of the chemical at concentrations of 0, 250, 500, 1000, 2000 and 4000 ppm (equivalent to 0, 47.5, 95, 190, 380 and 760 mg/m$^3$) for six hours plus T90 (12 minutes) per day, five days per week for 16 days. All rats exposed to 4000 ppm died on day one, and two males and three female rats exposed to 2000 ppm died on day four. Mean body weights of rats exposed to 2000 ppm were significantly less than those of chamber controls. Rats exposed to 2000 ppm that died early in the experiment were severely lethargic following daily exposure. Liver and kidney weights of all exposed groups were increased. Accumulation of minimal to mild hyaline droplets was observed in the renal tubular cortex of males exposed to concentrations of 250 to 2000 ppm (NTP, 2009; REACH).

In a study conducted in accordance with OECD TG 412, B6C3F1 mice (5/sex/dose) were exposed (whole body) to vapours of the chemical at concentrations of 0, 250, 500, 1000, 2000 and 4000 ppm (equivalent to 0, 47.5, 95, 190, 380 and 760 mg/m$^3$) for six hours plus T90 (12 minutes) per day, five days per week for 17 days. All mice exposed to 4000 ppm died on day one; all mice exposed to 2000 ppm died on day two; and four females exposed to 1000 ppm died by day four. Mean body weights of all exposed groups were similar to those of the chamber controls. Mice exposed to 2000 ppm were severely lethargic after the first exposure. The four females exposed to 1000 ppm that died early exhibited signs of lethargy and ataxia. Liver weights, both relative and absolute, were increased in all groups of surviving males and in 250 and 500 ppm female groups (NTP, 2009; REACH).

## Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. However, there is some evidence of genotoxicity for the metabolite α-methylstyrene oxide.

The potential genotoxicity of cumene has been studied in vitro in bacterial reverse mutation tests, mammalian cell gene mutation tests, an unscheduled DNA synthesis assay, and in vivo in mouse micronucleus tests. Four out of five bacterial reverse mutation assays were negative when tested with and without liver S9 activation enzymes; the remaining study had limited reporting details. Two out of three mouse micronucleus assays were negative apart from one study which did not report a dose-response relationship. All other study results were negative (REACH).

At least one metabolite of cumene, α-methylstyrene oxide, found in rats and mice, is mutagenic in bacteria (IARC, 2013).

## Carcinogenicity

The available data provide evidence of the carcinogenic effects of cumene, warranting classification as a carcinogen (see **Recommendation** section).

In a carcinogenicity study conducted in accordance with OECD TG 451, B6C3F1 mice (50/sex/group) were exposed to cumene vapour at concentrations of 0, 125 (females only), 250, 500, or 1000 (males only) ppm (equivalent to 0, 23.8, 47.5, 95 and 190 mg/m$^3$) for six hours plus T90 (12 minutes) per day, five days per week for 105 weeks. An exposure concentration-related decrease in survival was seen in males, and the survival of 1000 ppm males was significantly less than that of the chamber controls. Mean body weights of 1000 ppm males were generally less than those of the chamber controls after week eight of the study, and those of 500 ppm females were less from week 28 until week 76 of the study. The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of mice occurred with positive trends and were significantly greater than those in the chamber controls. The incidences of alveolar epithelial bronchiole metaplasia and bronchiole hyperplasia were significantly increased in all exposed groups of mice. In females, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends and were significantly increased in the 500 ppm group. In males, there were significant increases in the incidence of eosinophilic foci of the liver. In the nose, the incidences of olfactory epithelium atrophy, basal cell hyperplasia of the olfactory epithelium, atypical hyperplasia of the olfactory epithelium, hyperplasia of the olfactory epithelium glands, and suppurative inflammation were generally significantly increased in 500 and 1000 ppm males and 500 ppm females. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 500 ppm females. The incidence of basal cell hyperplasia was significantly increased in 250 ppm females (NTP, 2009; REACH).

In a carcinogenicity study conducted in accordance with OECD TG 451, Fischer F344 rats (50/sex/group) were exposed to cumene vapour at concentrations of 0, 250, 500 or 1000 ppm (equivalent to 0, 47.5, 95 and 190 mg/m$^3$) for six hours plus T90 (12 minutes) per day five days per week for 105 weeks. Treatment-related increases were observed in the incidence of nasal tumours (respiratory epithelial adenoma) in both males and females, and kidney tumours (renal tubule adenoma or carcinoma) in males. The increase in the incidence of nasal tumours (respiratory epithelial adenoma) was dose-related in males. An increase in renal tubule hyperplasia and papillary mineralisation were seen in males, with a linear pattern. In a subchronic study in rats with five exposure groups (62.5, 125, 250, 500 or 1000 ppm equivalent to 11.9, 23.8, 47.5, 95 and 190 mg/m$^3$), dose-related increases in the severity of proximal tubular hyaline droplet accumulation and regeneration were seen, together with increases in the incidence of medullary granular casts and in the levels of α2u-globulin in males. Males had a treatment-related increase in the incidence of testicular tumours (interstitial-cell adenoma). Tumours of the nasal cavity and splenic haemangiosarcomas are rare spontaneous neoplasms in experimental animals. While there are indications that the kidney tumours in male rats could be due to the species-specific effect of α-2u-globulin nephropathy, the International Agency for Research on Cancer (IARC) did not find sufficient evidence to suggest that any of the kidney tumours were species-specific (IARC, 2013).

## Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not cause specific reproductive or developmental toxicity. No changes were seen in the reproductive organs in rats exposed to cumene vapour for 13 weeks. In two well-conducted studies in rats and rabbits, no developmental effects were observed (EU RAR, 2001).

***Reproductive toxicity***

In a repeated dose toxicity study performed according to OECD TG 413 in compliance with good laboratory practice (GLP), Fischer 344 rats (15 males/group, number of females not reported) were exposed to cumene vapour at 0, 100, 500 and 1200 ppm (equivalent to 0, 19, 95 and 228 mg/m$^3$) for six hours per day, five days per week, for 13 weeks. No effects on sperm count, sperm morphology, spermatogenesis were observed (REACH; EU RAR, 2001).

***Developmental toxicity***

In a developmental toxicity study, groups of SD rats (25 females/group) were exposed to cumene vapour for six hours/day on gestational days 6–15 at target concentrations of 1, 100, 500 and 1200 ppm (equivalent to 0.19, 19, 95 and 228 mg/m$^3$). Scheduled sacrifices were performed on day 21. No dams died, aborted or delivered early. Three dams at 500 ppm and two dams each at 100 and 0 ppm were not pregnant. All pregnant dams had live litters (one or more live foetuses) on day 21. Maternal toxicity was observed at 500 and 1200 ppm as significant reductions in body weight gain (about 20 %), and treatment-related clinical signs of toxicity following daily exposures (perioral wetness and perioral encrustation) as well as during exposures (hypoactivity and blepharospasm), decreased food consumption during the exposure period and increased relative liver weight at necropsy. Reduced food consumption and clinical observations during exposure were also observed at 500 ppm. The no observed effect concentration (NOEC) for maternal toxicity was 100 ppm. The no observed NOEC for developmental toxicity (including teratogenicity) was the highest dose tested, 1200 ppm (EU RAR, 2001; REACH).

In a developmental toxicity study, NZW rabbits (15 females/group) were exposed to cumene vapour for six hours/day on gestational days 6–18 at concentrations of 0, 500, 1200 and 2300 ppm (equivalent to 0, 95, 228 and 437 mg/m$^3$). Maternal toxicity (two deaths, significant reductions in weight gain and food consumption during the exposure period, clinical signs of toxicity and a significant increase in relative liver weight) was observed at 2300 ppm and to a lesser extent at 500 and 1200 ppm. An aborted litter was observed at the highest dose. No treatment-related developmental toxicity was observed at any exposure concentration. The NOEC for developmental toxicity was at least 2300 ppm EU RAR, 2001; REACH).

### Other Health Effects

#### Neurotoxicity

Short-term exposure to the chemical may cause dizziness, headache, drowsiness, slight incoordination, and unconsciousness in humans (NTP, 2009).

Neurotoxicity effects are limited to non-specific central nervous system depression at high doses (500 ppm). These effects are readily reversible. Exposure to cumene vapour was neither neurotoxic nor ototoxic in Fischer 344 rats (EU RAR, 2001).

## Risk Characterisation

### Critical Health Effects

The identified critical health effect for risk characterisation is carcinogenicity. Cumene can also cause respiratory irritation and reversible neurotoxic effects.

### Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemical is reported to be used overseas in home maintenance and auto products in concentrations $\leq$ 5 % (US Household Products Database). Thus, consumers are not likely to be exposed to high levels of cumene vapour for prolonged periods of time, particularly if label instructions are followed. Therefore, the public risk from this chemical is not considered to be unreasonable.

### Occupational Risk Characterisation

Given the critical systemic long-term 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 an amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **Recommendation** section.

## NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

### Regulatory Control

#### Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

#### 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] |
|---|---|---|

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Harmful: may cause lung damage if swallowed (Xn; R65)* | May be fatal if swallowed and enters airways - Aspi. Cat. 1 (H304) |
| Irritation / Corrosivity | Irritating to respiratory system (Xi; R37)* | May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) |
| Carcinogenicity | Carc. Cat 2 - May cause cancer by inhalation (T; R49) | May cause cancer - Cat. 1B (H350i) |

[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.

## References

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

European Union Risk Assessment Report (EU RAR) 2001. Cumene (CAS No. 98-82-8). Accessed June 2016 at http://echa.europa.eu/documents/10162/c44474a0-e926-451d-9efd-810b230008f4

Galleria Chemica. Accessed June 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Hazardous Substances Data Bank (HSDB) Accessed June 2016 at https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm

International Agency for Research on Cancer (IARC) (2013). Cumene monograph. Accessed June 2016 at https://monographs.iarc.fr/ENG/Monographs/vol101/mono101-009.pdf

National Toxicology Program (NTP) 2009. NTP Technical Report on the toxicology and carcinogenesis studies of cumene (CAS No. 98-82-8) in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program Technical Report 542. Accessed in June 2016 at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr542.pdf

Organisation for Economic Cooperation and Development (OECD) 1996. SIDS Initial Assessment Profile (SIAP) on cumene (CAS No. 98-82-8). Accessed June 2016 at http://webnet.oecd.org/Hpv/UI/handler.axd?id=4d7ca7b7-7dd1-4ea2-9a73-b7cf54ae1d83

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed June 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Substances in Preparations in Nordic Countries (SPIN). Accessed June 2016 at http://195.215.202.233/DotNetNuke/default.aspx

United States (US) Department of Health& Human Services Household Products Database. Accessed June 2016 at https://householdproducts.nlm.nih.gov/about.htm

Last update 25 November 2016

Share this page