2-Pentanone, 4-methyl-: Human health tier III assessment

1 July 2016

CAS Number: 108-10-1

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 III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

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

Disclaimer

Acronyms & Abbreviations

Synopsis

The Tier II assessment of the chemical under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework, concluded that no further risk assessment would be required if the recommended changes to the Poisons Standard (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) and recommended changes to the hazard classification for the chemical were implemented.

The need for an amendment of the current scheduling entry for the chemical was referred to the Chemical Scheduling Delegate in December 2013 in relation to the critical systemic health effects associated with the chemical; namely acute inhalational toxicity, skin and eye irritation potential, respiratory irritation and carcinogenicity as well as the potential for use of the chemical in cosmetics and domestic products in Australia. The Advisory Committee on Chemical Scheduling (ACCS) informed the delegate that the existing scheduling of the chemical in the Poisons Standard (current at March 2014) remained appropriate and there were 'no compelling grounds on the basis of toxicity and carcinogenicity provided to the committee for a change in scheduling' (TGA, 2014). The difference in opinion between the ACCS and NICNAS was noted regarding the human relevance of the carcinogenicity findings in rats. Therefore, a human health Tier III assessment was considered necessary to further evaluate the carcinogenicity potential for members of the general public exposed to the chemical and determine whether there is a need for further risk mitigation; by considering the carcinogenic potential of the chemical in animals and its relevance to humans, along with expected levels of public exposure and any implications for public health.

This Tier III assessment considers the evidence for the carcinogenicity of the chemical, including a discussion of the relevance to human health, confirming that the chemical is a Category 3 carcinogen. There was insufficient evidence to dismiss the human relevance of carcinogenicity findings in rats as reported in the United States (US) National Toxicology Program (NTP) study. However, as part of this assessment, it was determined that further amendments to the Poisons Standard are no longer recommended for the chemical as the expected duration and route of exposure arising from the expected use of the chemical by the general public is consistent with the current entries in the Poisons Standard (refer to **Restrictions** section).

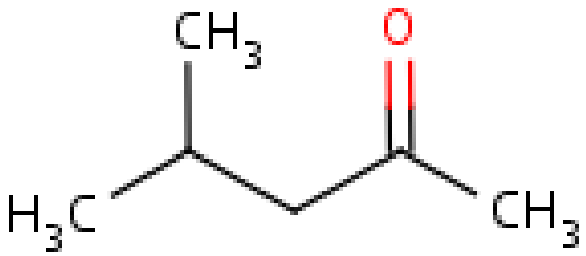
The Tier II human health IMAP assessment of the chemical is available at: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=88 and contains detailed assessment information that remains valid (NICNAS). New or updated information is included in the Tier III human health report, in the relevant sections. The Tier II and Tier III reports should be read together.

Rationale for Tier III Assessment

In order to confirm the Category 3 carcinogenicity classification of the chemical recommended as a result of the IMAP Tier II assessment and its relevance to humans requiring public health control measures (i.e. to amend the current scheduling entry in the SUSMP), NICNAS reviewed the carcinogenicity data and current public health control measures to determine whether the chemical should be referred again to the Chemical Scheduling Delegate for further consideration.

The carcinogenicity hazard classification recommended as part of the Tier II assessment of the chemical has been adopted by Safe Work Australia (SWA) and the chemical is listed on the Hazardous Substances Information System (HSIS) as a Category 3 carcinogen.

Chemical Identity

Synonyms	methyl isobutyl ketone MIBK 4-methyl-2-pentanone isopropyl acetone isobutyl methyl ketone
Structural Formula	
Molecular Formula	C6H12O
Molecular Weight (g/mol)	100.16
Appearance and Odour (where available)	Colourless liquid with a faint ketonic and camphor odour

SMILES

C(C)(=O)CC(C)C

Import, Manufacture and Use

Australian

The Tier II assessment identified only commercial use of the chemical in Australia (see Tier II report of the chemical).

International

The chemical has reported cosmetic (as a fragrance, solvent or denaturant) and domestic (in cleaning products for laundry and home, paints, lacquer and varnish, in modelling clay and finger paints, colour marker pens) uses (see Tier II report for the chemical).

The chemical also has reported commercial, site-limited and non-industrial uses (see Tier II report of the chemical).

Restrictions

Australian

The chemical is listed in Schedule 5 of the Poisons Standard (SUSMP, 2016).

'METHYL ISOBUTYL KETONE, **except** in preparations containing 25 per cent or less of designated solvents'.

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

Existing Work Health and Safety Controls

Hazard Classification

The chemical was listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia), with the following risk phrases for human health, prior to the IMAP Tier II assessment:

- Xn; R20 (acute toxicity);
- Xi; R36/37 (irritation); and
- Xi; R66 (skin dryness or cracking).

Following IMAP Tier II assessment, the following risk phrase for human health was added to the chemical (HSIS, Safe Work Australia):

- R40; Carcinogenicity Category 3 (Limited evidence of a carcinogenic effect)

Exposure Standards

Australian

The chemical has an exposure standard of approximately 205 mg/m^3 (50 ppm) time weighted average (TWA) and approximately 307 mg/m^3 (75 ppm) short-term exposure limit (STEL).

Exposure

Public Exposure

Based on the available information, the Australian public is exposed to the chemical through food and consumer products.

The International Agency for Research on Cancer (IARC) monograph for the chemical lists potential uses in cosmetic products, in denatured alcohol and as an excipient in drugs (IARC, 2012). Other reported uses include: as a synthethic flavouring substance, as a component of food packaging, in pharmaceutical manufacture, and used in the production of rubber tyres (HSDB).

The chemical is a naturally occurring compound that can be found in a variety of foodstuffs including orange and lemon juice, grapes, vinegar, cheeses, milk, beer, coffee, tea, mushrooms and some cooked meats (IARC, 2012). The following levels have been reported in food: 8 µg/kg in papaya, 10-120 µg/kg in beer, 6.5 mg/kg in coffee, with the following levels in packaged foods: 10.9 mg/kg in baked goods, 11.5 mg/kg in frozen dairy products, 2.6 mg/kg in meat products, 12.3 mg/kg in soft candy, 10.9 mg/kg in gelatins and puddings and 10.2 mg/kg in beverages (IPCS, 1990).

A number of consumer products containing the chemical are listed on the United States (US) Household Products Database, including:

- laundry stain remover;
- cleaning solution (for arts/crafts use);
- dry erase markers;
- denatured alcohol (concentration up to 10 %);
- aerosol paint/primer for art/craft or home maintenance (concentrations up to 8 %);
- auto product aerosol paint/primer (concentrations up to 12 %);
- liquid paint/lacquer/sealant for home maintenance or indoor use (concentrations up to 10 %);
- liquid paint thinner (concentration up to 35%)

The chemical is listed on the International Fragrance Association (IFRA) website as a fragrance ingredient. The chemical is also listed on the European Commission Cosmetic Ingredients and Substances database (CosIng) and identified for use as a solvent, denaturant and perfuming agent. Although specific cosmetic use in Australia could not be identified as part of the Tier II assessment for the chemical, it seems reasonable to assume that the chemical is present in cosmetic products based on the above evidence of use in cosmetic and domestic products overseas.

Based on product Safety Data Sheets sourced online, the chemical may be present in the following products in Australia:

- aerosol paints (concentrations found as high as 30 %);
- paint thinner (concentrations found as high as 15 %);
- sealant; and
- hardener (for paints) (concentrations found as high as 60 %).

Some of the above products may not be intended for domestic use. The concentrations quoted as found in the above products are not considered to be absolutely definitive as to a potential upper limit of concentration for the product types, or for domestic products in general, but are rather considered to be representative examples to confirm use of the chemical in products that are potentially available to Australian consumers.

Public exposure to the chemical may occur via the following exposure routes:

- oral (from food);
- dermal (from cosmetics and/or domestic products such as household cleaners);
- ocular (from cosmetics or aerosols/vapours); and
- inhalation (from aerosol paints and/or vapours from liquid products such as paint or domestic cleaning products).

Domestic products such as cleaners are unlikely to be used in significant concentrations or quantities on a regular and ongoing daily basis. Inhalation exposure may be a relevant exposure route, but the main source of exposure is expected to be dermal.

Daily use of cosmetic/fragrance products may occur and result in inhalational exposure to the chemical (and/or its vapour), but the use of the chemical in cosmetic/fragrance products is unlikely to occur in significant quantity as the odour of the chemical may provide a limiting factor.

Higher levels of inhalational exposure may occur in conjunction with the use of aerosol paints as compared to other domestic products, however, these are unlikely to be used by members of the general public on a regular and ongoing daily basis.

Similar to the findings of the IMAP Tier II report, the expected use pattern for members of the general public using products containing the chemical is considered unlikely to result in high levels of exposure on a regular ongoing and/or daily basis. Therefore the critical issue is whether the chemical has significant, previously unrecognised, carcinogenic potential.

Health Hazard Information

Carcinogenicity

The available data support the conclusion that the chemical has carcinogenic potential in animals, confirming the need for carcinogenicity hazard classification (Category 3) as recommended in the IMAP Tier II assessment. The potential for carcinogenicity is likely to have a threshold dose/concentration as the chemical is not considered to be genotoxic and the tumours observed in rats and mice in the studies conducted by the United States National Toxicology Program (US NTP) occurred only at high doses by inhalation exposure. The carcinogenic potential of the chemical could not be completely ruled out for humans. No oral or dermal carcinogenicity studies are available in animals.

The International Agency for Research on Cancer (IARC) evaluated the carcinogenicity potential of the chemical in 2012 and classified it as a Group 2B carcinogen—possibly carcinogenic to humans (IARC, 2012).

The US NTP has published toxicology and carcinogenicity studies conducted in Fischer 344/N (F344/N) rats and B6C3F1 mice for the chemical, which were considered as part of the IARC evaluation. Animals were exposed to 0, 450, 900 or 1800 ppm (approximately 1843, 3686 or 7373 mg/m^3) of the chemical via inhalation (whole body) for six hours per day, five days per week for either 104 (rats) or 105 (mice) weeks (US NTP, 2007; REACH).

Carcinogenicity findings in rats (US NTP, 2007)

The authors concluded that there was 'some evidence of carcinogenic activity' in male F344/N rats based on increased incidences of renal tubule neoplasms (specifically renal tubule adenoma and renal tubule adenoma or carcinoma combined). In addition, the increased incidence of mononuclear cell leukaemia in high dose male rats 'may have been related' to treatment with the chemical. The authors further concluded that there was 'equivocal evidence of carcinogenic activity in female F344/N rats based on the occurrence of renal mesenchymal cell tumours' in the high dose group (specifically malignant mesenchymal tumours). Other relevant findings from the carcinogenicity study in rats included chronic progressive nephropathy (CPN) in all

high dose males (with increased severity in males) and 70-88 % of exposed females, and a significantly increased incidence of adrenal medulla hyperplasia in high dose males.

There is some evidence that the renal tubule neoplasms observed in male F344/N rats is the result of accumulation of the α_{2u}-globulin protein and associated nephropathy; a well established carcinogenic mode of action that is specific to male rats and is not considered relevant to humans.

Summarising the results observed in rats, the IARC (2012) reported, 'Treatment-related increases in the incidence of kidney tumours were observed in males and females (renal tubule adenoma and carcinoma combined in males and two malignant mesenchymal tumours in high-dose females), together with concurrent treatment-related increases in the incidence of renal tubule hyperplasia and papillary mineralisation (which had a linear pattern) in males'.The IARC determined that the strength of evidence for the α_{2u}-globulin mechanism was 'weak', as not all the criteria for the α_{2u}-globulin mode of action were fulfilled by the data available for the chemical that was considered by the agency at the time of the 2012 evaluation. The agency noted that:

- the tumour response in male rats from the NTP study was weaker than would be expected for α2μ-globulin mediated nephropathy;
- the two year study observed an increase in incidence of chronic progressive nephropathy in both sexes (increased severity in treated males) and one subchronic inhalation study showed increased kidney weights in both sexes at the high dose (i.e. the effect was not male-specific); and
- the tumour response in the NTP study correlated best with the severity of chronic nephropathy.

However, a study conducted after the IARC evaluation reported that the chemical reversibly binds to α_{2u}-globulins (in vitro) to induce α_{2u}-globulin nephropathy, evidence supporting the male rat renal tumours being not relevant to humans (Borghoff et al., 2015). Rats (F344; n = 84/sex) were exposed via inhalation (whole body) to doses of 0, 450, 900 or 1800 ppm for six hours/day for either four days or four weeks. The severity of CPN was increased in male rats after four weeks of exposure to the chemical at doses of 900 ppm and above. There was no change in the severity of this lesion for female rats during this study. Hyaline droplet accumulation was observed in males (staining confirmed these as α_{2u}-globulin), but not in females. Lesions in females associated with CPN were negative for hyaline droplets. There was a concentration-dependent increase in the amount of α_{2u}-globulin in male rats only. In vitro evidence showed reversible binding of the chemical to α_{2u}-globulin, a criterion necessary to initiate α_{2u}-globulin nephropathy. The study authors, therefore, concluded that the chemical is an inducer of α_{2u}-globulin nephropathy, supporting the conclusion that male rat renal tumours are not relevant to humans (Borghoff et al., 2015).

The weight of evidence suggests that kidney tumours observed in male rats are at least partially attributable to the α_{2u}-globulin mechanism of action. However, as reversible binding of the chemical to α_{2u}-globulin has not been demonstrated in vivo, and the tumour incidence in the two year carcinogenicity study correlates more to the severity of CPN, it is still possible that there is more than one contributing mechanism.

The NTP study also showed a significantly increased incidence of mononuclear cell leukaemia in high dose male rats that 'may be related' to exposure to the chemical. The incidence in the control group was comparable with historical control ranges for this condition. As the increased incidence of leukaemia was of statistical significance only in the high dose group, the study authors determined that the strength of the evidence did not allow for a definitive relationship between exposure and response. As this finding could not be ruled out as being related to treatment, it is assumed that the finding is relevant to humans.

The renal mesenchymal cell tumours observed in female rats receiving the high dose in the NTP study were at a low incidence (2/50 animals). The tumour type (renal mesenchymal tumour) is reported as a rare tumour type, and whilst the incidence of the tumour type was low in the NTP study, the incidence was outside the range of historical control data for the laboratory at the time of the study. The incidence of chronic nephropathy was also significantly increased in treated females (US NTP, 2007). As the renal findings in female rats from the NTP study cannot be ruled out as being related to treatment with the chemical, it is assumed that the findings are relevant to humans.

Carcinogenicity findings in mice (US NTP, 2007)

The authors of the two-year NTP study in mice concluded that the results provided 'some evidence of carcinogenic activity' for the chemical, which was based on the increased incidence of liver neoplasms (specifically hepatocellular adenoma and hepatocellular adenoma or carcinoma combined) in high dose male and female mice. It should be noted that there is a high background incidence of this tumour type in mice.

In a seven-day study, male mice (n = 6/dose) were exposed via whole body inhalation to the chemical at a concentration of 1800 ppm for six hours per day. A detailed analysis of gene expression in the liver showed an increase in certain cytochrome P450 (or CYP, in this case specifically CYP2B10) transcription (approximately 4 fold) and decreased CYP4A10 (approximately 5.5 fold) transcription. An increase in CYP2B10 activity was observed, along with hepatocyte proliferation (slight hepatocellular hypertrophy with increased cytoplasmic eosinophilia). Based on these results, it has been suggested that the chemical may be a constitutive androstane receptor (CAR) agonist (REACH).

The IARC (2012) stated that 'There was no evidence that the tumours arose from a cytotoxic-regenerative cell proliferation mechanism as no overt toxicity occurred in the livers of exposed mice.' and 'The strength of evidence that male and female liver tumours arose through a nuclear receptor mechanism is weak. The relevance of the tumour response to humans cannot be excluded.'

The mechanism of action for CAR agonists is well established (Elcombe et al., 2014) and consists of the following key events (presented in order):

- CAR activation;
- altered gene expression;
- increased cell proliferation;
- clonal expansion leading to altered foci; and
- liver adenoma/carcinoma.

Associated events include altered epigenetic changes, CYP2B induction (indicative of altered gene expression), liver hypertrophy (indicative of increased cell proliferation) and inhibition of apoptosis (inhibition in altered foci may enhance lesion growth and tumour formation).

The seven-day study above indicates that the chemical can induce CYP2B enzymes through altered gene expression and showed increased cell proliferation (REACH). The studied CAR agonists induce CYP2B enzymes; however, activation of alternative receptors may also increase CYP2B activity (Elcombe et al., 2014). Results in some short term repeated dose toxicity studies conducted with the chemical have shown increases in absolute and/or relative liver weights and liver hypertrophy. Phenobarbital (PB), a well studied CAR agonist, causes increases in liver weights via both liver hypertrophy and hyperplasia (Elcombe et al., 2014).

The two-year NTP study conducted with the chemical showed an increase in eosinophilic foci in all groups (although only statistically significant in females at doses of 450 and 1800 ppm) but no evidence of liver hypertrophy (US NTP, 2007). Studies with PB have shown that liver hypertrophy may not be evident in longer-term studies; however, the rate of cell proliferation may be enhanced in altered hepatic foci (Elcombe et al., 2014). Therefore, the lack of liver hypertrophy in the two year NTP study does not provide sufficient evidence to dismiss the CAR agonist mechanism of action for the chemical. It appears that the increased incidence of males with eosinophilic foci observed in the NTP study in mice treated with the chemical is not statistically significant (or not significantly different from controls), and the significance in females does not appear to follow a dose-response relationship (as the incidence in the 900 ppm group was not significantly different from controls). It is also noted that the number of animals presenting at necropsy with eosinophilic foci was lower than those presenting with liver adenoma and/or carcinoma.

In a ten-day study, mice (B6C3F1, C57BL/6 and CAR/PXR knockout) were exposed via inhalation to the chemical at a concentration of 0 or 1800 ppm for six hours per day, five days per week. Standard laboratory strain mice (B6C3F1 and C57BL/6) in the 1800 ppm groups showed increased liver weights with accompanying hepatocellular hypertrophy and increased mitotic figures. Increased levels of gene expression were observed in this group; increases in CY2B10 and CYP3A11 gene transcripts were observed, but no increases in CYP1A1 or CYP4A10 gene transcripts. No induction of S-phase DNA synthesis or CAR/PXR activation was observed in knockout mice (REACH).

The evidence suggest the chemical is a CAR agonist. Liver tumours observed in mice are consistent with the CAR agonist (PB-like) mode of action and are therefore considered to be not relevant to humans.

Overall weight of evidence consideration for carcinogenicity

The weight of evidence suggests that the carcinogenic potential of the chemical should be considered as applicable to humans, based on the following:

- Findings in the NTP chronic/carcinogenicity studies in rats and mice—renal tubule adenoma/carcinoma in male rats ('some evidence of carcinogenic activity'), mononuclear cell leukaemia in male rats ('may have been related to treatment'), renal mesenchymal cell tumours in female rats ('equivocal evidence of carcinogenic activity') and hepatocellular adenoma/carcinoma in male and female mice ('some evidence of carcinogenic activity');
- The lack of genotoxic potential for the chemical indicates a non-genotoxic mode of action;
- The evidence suggests that the renal tubule adenoma/carcinoma may be partially attributed to an α_{2u}-globulin mediated toxicity which is specific to male rats and is not relevant to humans. However, the possibility that this mechanism could be a confounding factor masking another mechanism for renal tubule adenoma/carcinoma has not been completely discounted (based on an increased incidence of CPN) in treated female rats and the lack of definitive evidence of irreversible binding of the chemical to α_{2u}-globulin in vivo);
- The evidence supports the conclusion that the hepatocellular adenoma/carcinoma finding in mice can be attributed to activation of the CAR;
- There remains limited evidence for treatment-related carcinogenicity in one species (renal tumours and mononuclear cell leukaemia in male rats and renal mesenchymal tumours in female rats), which is considered sufficient for classification of the chemical as a Category 3 carcinogen according to the Approved Criteria (SWA, 2004) and a Category 2 carcinogen according to the GHS (2009).

This Tier III assessment concludes that the carcinogenicity findings in rats exposed to the chemical are relevant to humans and that the chemical is appropriately classified as a Category 3 carcinogen according to the Approved Criteria (SWA, 2004). The chemical is considered to have low carcinogenic potential.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (carcinogenicity);
- systemic acute effects (acute toxicity from inhalation exposure); and
- local effects (skin, eye and respiratory irritation).

The chemical has an existing hazard classification for acute inhalational toxicity, eye and respiratory irritation and carcinogenicity. For more information on the hazards associated with the chemical, please see the Tier II risk assessment.

Local effects (eye and respiratory irritation) occurred in short term exposure studies. Eye irritation has been observed following 15 minutes of exposure to an atmosphere containing the chemical at a concentration of 200 ppm (approximately 820 mg/m^3) in human volunteers (IPCS, 1990). Symptoms of respiratory irritation have been recorded in humans exposed to a concentration of 100 ppm (approximately 410 mg/m^3), with irritation of the nose and throat reported following two hours of exposure to the chemical at a concentration of 10 mg/m^3 (IPCS, 1990). A more recent study in human volunteers concluded that the mean threshold for odour detection was 10 ppm, but the mean threshold for lateralisation (sensory irritation) was 8874 ppm (HSDB).

Systemic acute effects occurred in acute exposure studies. Symptoms of intoxication in humans following acute inhalation exposure to the chemical included a transient anaesthetic effect. Following exposure to the chemical for two hours at a concentration of 10, 100 or 200 mg/m^3 (approximately 2.4, 24.4 or 48.8 ppm) during light exercise, symptoms in human volunteers included headache and/or nausea and/or vertigo (IPCS, 1990). One study indicated that the odour of the chemical was 'objectionable' at a concentration of 200 ppm or approximately 410 mg/m^3 (CIR, 2004).

Systemic long term effects, namely carcinogenicity occurred in rats and mice following repeated inhalational exposure at high levels (of 900 ppm and 1800 ppm in rats, approximately 3686 and 7373 mg/m^3 and 1800 ppm or approximately 7373 mg/m^3 in

mice) (NTP, 2007; REACH). For additional details please see the **Hazards** section of this Tier III report. The current exposure standards for workers using the chemical are much lower than the doses associated with carcinogenic effects in animal studies.

The purpose of the Tier III risk assessment of the chemical was to determine the risk to the general public of systemic long term effects arising from the expected pattern of exposure and whether additional regulatory controls (such as changes to the Poisons Standard) were required to sufficiently mitigate the risk of carcinogenicity.

The above information indicates that the short-term systemic acute effects and local health effects occur at lower doses than the systemic long-term health effect of carcinogenicity.

Public Risk Characterisation

This Tier III assessment has determined that the carcinogenic risk to the general public arising from the expected use of the chemical is low.

The hazard information for the chemical indicates that acute toxic effects and local irritant effects occur at lower doses than potential carcinogenicity and may place a practical limit on the level of exposure that would be tolerated by members of the general public using products containing the chemical.

The expected exposure pattern associated with use by the general public is unlikely to result in regular ongoing exposure to high levels of the chemical sufficient to cause a concern for carcinogenicity:

- Domestic products such as cleaners are unlikely to be used in significant quantities above levels causing sensory irritation. Inhalation exposure is not expected to be the primary exposure route. Use of products containing the chemical, particularly in poorly ventilated areas, may result in local irritant and other transient acute health effects (such as headache, nausea, vertigo) at doses much lower than those associated with carcinogenicity in animal studies. Whilst products may be used regularly, daily use resulting in high levels of systemic exposure is not reasonably expected to occur with this product type.

- Daily use of cosmetic/fragrance products may occur and is expected to result in some inhalational exposure to the chemical, but use of cosmetic/fragrance products is unlikely to occur in significant quantity to cause a concern for carcinogenicity as the local health effects (nose, throat, respiratory irritation) of the chemical are considered likely to be a limiting factor for consumer usage.

- Higher levels of inhalational exposure may occur in conjunction with the use of aerosol paints; however, these are unlikely to be used by members of the general public on a regular and ongoing daily basis. Again, the short term health effects (such as nose, throat, or respiratory irritation) are considered likely to create a limit to the level of exposure that could be tolerated during product use.

The carcinogenic effects associated with the chemical occurred following high levels of regular exposure on a long-term basis. Although products used in a domestic setting may contain significant concentrations of the chemical (particularly concentrations above the 25 percent cut-off for inclusion in Schedule 5) these products are unlikely to be used on a frequent long-term basis. Domestic products that are potentially used on a frequent basis (such as cosmetics) are unlikely to contain concentrations of the chemical that would cause concern for acute and/or local health effects which occur at lower concentrations than potential carcinogenic effects. The current exposure standards for the chemical are much lower than the doses associated with carcinogenic effects in animal studies, suggesting that protecting workers from the short-term health effects provides adequate protection from long-term health effects. It is generally assumed that industrial and/or commercial use of the chemical will result in higher levels of exposure occurring more frequently than cosmetic or domestic use of the chemical. Based on a consideration of the above, it has been determined that recommended changes to the current poisons scheduling of the chemical is not warranted.

The Tier III IMAP assessment concludes that the current entries for the chemical in the Poisons Standard provides sufficient risk mitigation for the general public using products containing the chemical.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

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
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)].

[*] 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

The advice provided in the human health Tier II IMAP report remains unchanged.

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

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