Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

2-Butanone, oxime (MEKO)

Evaluation statement

14 December 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

2-Butanone, oxime (MEKO)

Chemical in this evaluation

Name	CAS registry number
2-Butanone, oxime	96-29-7

Reason for the evaluation

New information is available about human health risks.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified consumer and industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

Information about the introduction, use and end use of the chemical in Australia is limited. Information indicates use in sealant and adhesive products.

Internationally, the chemical has reported domestic and commercial uses in alkyd paints, lacquers, varnishes, adhesives, and sealants. The concentration in alkyd paint is typically <1%. Maximum concentrations of 5% and 2% have been identified for sealants and adhesives, respectively.

Furthermore, the chemical is used as a corrosion inhibitor and serves as an intermediate in chemical processes.

The chemical has non-industrial uses in wood preservatives and antifouling marine paints.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. The previous assessment of 2-butanone, oxime should be read in conjunction with this evaluation statement (NICNAS 2013). This evaluation statement reviews new evidence on skin irritation,

systemic target organ toxicity for single exposure and repeated exposure, and carcinogenicity.

Based on the toxicokinetic studies the chemical is well absorbed, distributed, metabolised and excreted.

The available data suggest that the chemical is not expected to:

- have genotoxic potential
- cause specific adverse effects on fertility/sexual function and foetal development.

Based on the available data the chemical has moderate acute oral and dermal toxicity and low acute inhalation exposure. Data from acute oral, inhalation and dermal toxicity testing in rats and rabbits also indicate that the chemical causes strong transient narcotic effects in both sexes following a single exposure.

Based on the weight of evidence from available animal data, the chemical has the potential to cause damage to the nasal epithelium after oral and inhalation exposure. While there is no relevant information provided from acute toxicity studies, a repeat dose toxicity study indicates that the chemical may cause irreversible damage to the nasal epithelium after only a few exposures at relatively low doses. Degeneration of the nasal epithelium was observed at 108 mg/m^3 after 5 exposures. In longer term studies effects on the nasal epithelium were observed at lower doses, with a no observed effect concentration of 10.8 mg/m^3 established.

Based on the weight of evidence and the persistence of skin irritation effects observed, the chemical is considered to be a skin irritant.

Based on the available data, the chemical is expected to cause serious systemic health effects on the blood system following repeated oral and inhalation exposure. Dose related effects were observed in rats and mice in both oral and inhalation studies. These effects were also noted in the developmental toxicity studies in rats and rabbits and in a two-generation toxicity study in rats. The chemical is a methaemoglobin inducer, leading to regenerative anaemia (methaemoglobinaemia). A marked increase of haemosiderosis in the spleen in combination with other changes indicated significant haemolytic anaemia following repeated exposure to the chemical.

There is sufficient evidence that the chemical has carcinogenic effects in animals. Liver tumours following inhalation exposure have been observed in two species (rats and mice). There was clear evidence of progression to malignancy of liver tumours. Female rats and mice were less sensitive than males in the available studies. There was some indication of a multi-site response due to the increased incidence of benign fibroadenoma observed in male rats. The mode of action for carcinogenicity of the chemical is uncertain and the availability of mechanistic data is limited. The available data support a likely threshold mode of action. As there is no established mechanism to determine the carcinogenicity of the chemical, the relevance to humans cannot be ruled out.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety, as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 3	H301: Toxic if swallowed
Acute toxicity – dermal	Acute Tox. 4	H312: Harmful in contact with skin
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Specific target organ toxicity (single exposure)	STOT SE 3	H336: May cause drowsiness or dizziness
Specific target organ toxicity (single exposure)	STOT SE 1	H370: Causes damage to organs - upper respiratory tract
Specific target organ toxicity (repeat exposure)	STOT RE 2	H373: May cause damage to organs through prolonged or repeated exposure - blood system
Carcinogenicity	Carc. 1B	H350: May cause cancer

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical:

- at concentrations up to 1% in paint
- at concentrations up to 5% in sealants
- by inhaling aerosols or vapours from DIY products.

Due to infrequent domestic use of the paints and sealants the critical health effects for the public are expected to be acute or short-term effects. Based on the available data, the chemical may cause damage to the nasal epithelium after short term exposures. Using the lowest adverse effect concentration (LOAEC) for acute systemic toxicity (108 mg/m^3), the margin of exposure (MOE) levels for the use of the chemical in alkyd paint and sealants are 0.5 and 1, respectively. The MOE value estimates the likelihood that an adverse health effect will occur under the conditions of exposure.

The calculated values for margin of safety indicate there is a risk to the public that requires management (see **Proposed means for managing risks** section). Information from a journal article on exposure and emission of the chemical shows that high rate of ventilation significantly reduces the concentration of the chemical in air. Therefore, use of adequate ventilation would reduce exposure and hence minimise the risk to the public. The risk could be managed by amending the information on the chemical in the Poison Standard.

Workers

Potential exposure of workers to the chemical may occur via inhalation, dermal or ocular route. Given the identified long-term and acute systemic effects, local health effects and carcinogenic effects of the chemical, control measures to minimise dermal, ocular and

inhalation exposure are needed to manage the risks to workers (see **Proposed means for managing risk** section).

The data available, including overseas exposure standards, indicate that a workplace exposure standard may be beneficial to mitigate the risk to workers. The data available indicate that a workplace exposure standard (WES) may be beneficial to mitigate the risk of adverse effects to workers. Degeneration of the nasal epithelium has been observed in inhalation studies in animals. The chemical has also carcinogenic effects in animals following inhalation exposure. No human data are available. Internationally exposure standards have been established.

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling amends the entry for the chemical in the *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons)* (SUSMP).

It is recommended that to manage the potential risk associated with the use of these chemicals that:

- the entry results in labelling requirements that provides safety direction to use only in a well-ventilated area
- the appropriateness of the current concentration exemptions are considered.

Consideration should be given to the following:

- the likely wide-spread use of this chemical in paint and sealant products in Australia
- exposure to the chemical causes severe effects to respiratory system after only a few exposures
- restrictions in Europe that limits sale of the chemical to the general public if the concentration is ≥0.1% in substances and preparations
- proposed Canadian risk management to limit the concentration of MEKO in:
    - paints to 0.0032–0.55% (depending on paint type)
    - sealants to 0.2–0.42% (depending on sealant type)
- a Canadian code practice recommending to:
    - reduce the concentration of butanone oxime in interior and dual use consumer alkyd paint and coating products to the lowest level technically and economically feasible
    - to increase ventilation in the work area during painting
    - to continue ventilation after painting.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia consider establishing a workplace exposure standard.

It is recommended that Safe Work Australia update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from oral, dermal, ocular and inhalation exposure to the chemical 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
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS, and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

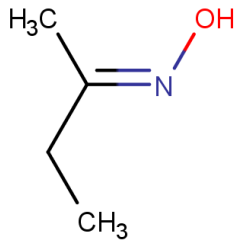
The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	2-Butanone, oxime
CAS No.	96-29-7
Synonyms	methylethyl ketoxime
Molecular formula	C4H9NO
Molecular weight (g/mol)	87.12
SMILES	ON=C(C)CC
Chemical description	Although two geometrical isomers are possible for butanone oxime, the *trans* isomer predominates (>99%) (OECD 2003).
Structural formula	

Relevant physical and chemical properties

Physical form	Clear colourless liquid
Melting point	-29.5 °C
Boiling point	152.5 °C
Vapour pressure	140-1070 Pa at 20 °C
pKa	12.45 at 25 °C
log K_{ow}	0.63 at 25 °C

Introduction and use

Australia

Australian introduction and use have been described in the previous assessment of 2-Butanone, oxime (MEKO) (NICNAS 2013). The chemical has reported domestic use in adhesives and binding agents.

Based on an application to amend the entry in the SUSMP (TGA 2015) it is likely that there are silicone adhesive and sealant preparations containing up to 2.5% of the chemical being introduced into Australia.

International

The following international uses have been identified through the previous assessment of the chemical (NICNAS 2013), the Government of Canada report 2010, the United States Environmental Protection Agency (US EPA) Chemical Data Reporting 2016 and 2020; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; the Substances and Preparations in Nordic countries (SPIN) database; Consumer Products Information Database.

The chemical is mostly used as an anti-skinning agent, which prevents the drying and formation of a skin on the surface of paint and coating products. It is used in the formulation of alkyd paints, varnishes, stains, finishes, coatings, adhesives and sealants for both commercial and domestic use and consumer use. The concentration in alkyd paint is typically <1%. Maximum concentrations of 5% and 2% have been identified for sealants and adhesives, respectively.

The chemical has other reported commercial uses in:

- corrosion inhibitors
- insulating materials
- solvents
- viscosity adjustors
- fuel additives.

The chemical has reported site-limited use as an intermediate in chemical processes.

The chemical has non-industrial uses in antifouling paints and wood preservatives.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

The chemical is listed in the *Poisons Standard – The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) under Schedule 6 (TGA 2023). The Schedule 6 entry states:

'METHYL ETHYL KETONE OXIME except:

(a) in viscous silicone adhesives or viscous silicone sealants containing 2.5% or less of methyl ethyl ketone oxime; or

(b) in other preparations containing 1% or less of methyl ethyl ketone oxime'.

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

Workers

The chemical is currently listed on the HCIS (SWA) with the following hazard categories and statements for human health:

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H312: Harmful in contact with skin
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Carcinogenicity	Carc. 2	H351: Suspected to cause cancer

International regulatory status

Exposure standards

The following exposure standards are identified (Chemwatch):

- Germany workplace exposure limit (TRGS 900): 1 mg/m^3 (0.3 ppm)
- US AIHA Workplace Environmental Exposure Levels 8-hour TWA: 10 ppm
- US Toxicology Excellence for Risk Assessment Workplace Environmental Exposure Levels 8 hour TWA: 10 ppm.

The German workplace limit is derived from the no observed adverse effect concentration of 10.8 mg/m^3 established in a 13 week inhalation study in male CD-1-mice (see **Repeat dose toxicity**) (ECHA 2014).

Canada

Code of Practice for 2-butanone, oxime (butanone oxime) Associated with the Interior Application of Consumer Alkyd Paint and Coating Products (the Code).

The Code identifies three recommended practices:

- to reduce the concentration of butanone oxime in consumer interior alkyd paints and coatings to the lowest level technically and economically feasible
- to incorporate the labelling statement, “use only in a well-ventilated area”, on all applicable consumer interior and dual use alkyd paints and coatings

- to implement a consumer education program that will inform consumers on behaviours that will help to achieve well ventilated conditions during and following interior application of all applicable consumer interior and dual use alkyd paints and coatings.

Proposed new risk management actions for 2-butanone, oxime:

The proposed regulatory approach may include restricting the concentrations of butanone oxime in the products of concern that are available to consumers, namely paints and coatings; stains and finishes; and adhesives and sealants. Canada's proposed concentration limits for the products of concern are listed in Table 1.

Table 1 Proposed concentration limits in Canada

Product type	Proposed concentration limit (% w/w)
Interior or dual use non-spray paints, coatings, stains and finishes (including primers, varnish and polyurethane)	0.0032
Exterior non-spray paints, coatings, stains, and finishes (including primers, varnish and polyurethane)	0.18
Interior or dual use spray paints and coatings	0.048
Exterior spray paints and coatings	0.55
Interior or dual use gasketing adhesives and silicone sealants	0.2
Exterior silicone sealants	0.42

The chemical is listed on the Canadian toxic substance list: schedule 1 (CEPA).

European Union

The chemical is listed on 'EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products - Annex II - List of Substances Prohibited in Cosmetic Products' (EC).

The chemical is restricted by Annex XVII to REACH Regulations. The chemical cannot be used in substances and preparations placed on the market for sale to the general public if the concentration is ≥0.1% (European Parliament and Council 2021; European Parliament and Council 2023).

New Zealand

The chemical is listed on 'New Zealand Cosmetic Products Group Standard - Schedule 4 - Table 1: Components Cosmetic Products must not contain' (EPA).

Asia

The chemical is listed on 'ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products' (HSA 2019).

Human exposure

Workers

The primary occupational exposure to the chemical is via inhalation from its use as an anti-skinning agent in the formulation of alkyd paints, varnishes, stains and coatings. Limited published measured data for workplace exposure are available. Measured data collected in Germany from 1998 to 2011 indicate concentrations (95th percentile) for relevant activities (laying wood floors, surface coating, brushing and rolling and spray painting) of 1.1–5.4 mg/m^3. However, the air monitoring data may not reflect the current situation at the workplaces, due to significant changes in the currently used formulations of paints and varnishes containing the chemical (DGUV 2013; ECHA 2014).

Public

Potential dermal, ocular, and inhalation exposure of the public may occur during domestic use of paints, coatings and adhesives containing the chemical (see **Introduction and use**).

Health Canada has modelled the inhalation exposure to vapours from paints and sealants containing MEKO using ConsExpo v. 4.1 software (Government of Canada 2010). Based on product scenario modelling using ConsExpo, the highest air concentrations resulted from inhalation during the use of alkyd paints and coatings and were in the range of 73–223 mg/m^3. The lowest estimated air concentration according to ConsExpo modelling was derived for the use of the chemical at 2% concentration in adhesives with 3.39 mg/m^3. It is noted that inhalation exposure may be underestimated as exposure to vapour is not considered in the ConsExpo spray model (RIVM 2007). Using the Wall Paint Exposure Assessment Model, an 8 hour average air concentration of 195 mg/m^3 was derived for alkyd paints (Government of Canada 2010).

A US study of consumer exposure to MEKO (Chang 1998) predicted a maximum concentration of MEKO in indoor air of 18 mg/m^3 based on the use of alkyd paint containing 0.293% w/w MEKO. Peak concentration >80 mg/m^3 were identified. The air concentrations were shown to be significantly affected by:

- the concentration in the paint (peak concentration reduced by more than 80% for paint containing 0.096% compared with paint containing 0.293%)
- increasing ventilation.

A limited unpublished study measured MEKO concentrations of up to 9.9 ppm (30 mg/m^3) during a simulation using an indoor painting scenario with an alkyd paint containing approximately 0.2% MEKO (Government of Canada 2010).

Health hazard information

The previous assessment of the chemical should be read in conjunction with this evaluation statement (NICNAS 2013). This evaluation reviews new data available for the chemical relating to toxicokinetics, acute toxicity, skin irritation, carcinogenicity, and repeated dose toxicity.

More information used to draw conclusions for skin sensitisation, skin and eye irritation, and developmental and reproductive toxicity is available in the previous assessment report (NICNAS 2013).

Toxicokinetics

The chemical is reported to be well absorbed, metabolised and excreted following oral exposure, intravenous administration and dermal exposure in animals (NICNAS 2013). Based on adverse effects reported in acute and chronic inhalation toxicity studies the chemical is considered to be well absorbed and distributed (see **Acute toxicity** and **Repeat dose toxicity**).

In a toxicokinetic study, pregnant mice received a single oral dose of radiolabelled MEKO. The highest levels of radioactivity were found in the nasal epithelium and the liver. Accumulation in the nasal epithelium was rapid and high concentrations of radioactivity were found at all time intervals studied (ECHA 2017).

The biotransformation of the chemical was studied in liver microsomes and cytosol from male and female rats, mice and several human liver samples. The chemical reactivity of the postulated metabolites was characterised (ECHA 2017). The chemical was found to be oxidised to butane-2 nitronate by microsomal monooxygenases but at very low rates. No sex differences in the rates of microsomal oxidation of the chemical to butane 2-nitronate were noted.

The toxicokinetic studies demonstrated the existence of two and suggested a possible third metabolic pathway for the chemical in the rat, the major pathway being the hydrolysis of the chemical to methyl ethyl ketone. One of the minor pathways appears to be a P450 mediated oxidation of the chemical to butane-2 nitronate and the second a reduction of the chemical. No quantitative sex differences in these pathways were identified (ECHA 2017).

Acute toxicity

Lethality

Based on available data the chemical has medium acute oral toxicity. In the previous assessment of the chemical (NICNAS 2013), the reported LD50 values from acute toxicity studies were >2000 mg/kg bw. However, mortality was observed within 48 hours of dosing in a rabbit developmental toxicity study. The reported acute toxicity point estimate was 100 mg/kg bw (ECHA 2018). Therefore, based on the derived acute toxicity estimate value, classification of the chemical for acute oral toxicity Category 3 is warranted.

In a rabbit developmental study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guidelines (TG) 414 (ECHA 2018), New Zealand White (NZW) rabbits were administered 0, 10, 20, 40 or 80 mg/kg bw/day in the preliminary study (5 females/dose) and 0, 8, 14, 24 or 40 mg/kg bw/day in the main study (18 females/dose).

In the preliminary study, mortality was observed (2/5 females) within 48 hours of receiving 80 mg/kg bw/day (cumulative dose of 160 mg/kg bw/day). After 4 days, following a cumulative dose of 320 mg/kg bw/day there were no surviving females. Mortality was also observed at the 40 mg/kg bw/day in both the preliminary study (2/5 females, GD 10–11) and the main study (8/18 females, GD 11–24). At 40 mg/kg bw/day clinical signs if toxicity included decreased activity, laboured breathing, reddish coloured fluid in the bottom of the cage and decreased body weight. Brown discolouration of the lungs was noted, as were fluid contents in the thoracic cavity, pale liver, accentuated lobular markings on the liver, dark red contents in the urinary bladder and thickened mucosa. An LD50 was not determined but a converted acute toxicity point estimate of 100 mg/kg bw was calculated (ECHA 2018).

Based on previously assessed data the chemical has moderate acute toxicity following dermal exposure and low acute toxicity following inhalation exposure (NICNAS 2013). No new data have been identified.

Systemic target organ toxicity – single exposure

Narcotic effects

Data from acute oral, inhalation and dermal toxicity testing in rats and rabbits have shown strong transient narcotic effects in both sexes following single exposure to the chemical. The observed narcotic effects warrant hazard classification of the chemical as STOT SE Category 3 that may cause drowsiness or dizziness.

In an acute neurotoxicity study, SD rats (10/sex/dose) received a dose of 0, 100, 300 or 900 mg/kg bw of the chemical. There was no mortality in any dose group. At doses of ≥300 mg/kg bw, animals displayed transient effects of impaired gait and disturbed aerial righting reflex. At 900 mg/kg bw, statistically significant decreases in motor activity were reported within one hour of exposure (ECHA 2018).

In an acute dermal study, the chemical was applied to the skin of NZW rabbits (5/sex/dose) at doses of 0, 18, 185 or 1848 mg/kg bw. No animals survived at 1848 mg/kg bw. Transient narcotic effects were noted from the lowest dose of 18 mg/kg bw during the first 48 hours following exposure. At the next dose of 185 mg/kg bw, these effects were considered significant (ECHA 2018).

In an acute inhalation study, Fischer (F344) rats (5/sex/concentration) were exposed to the chemical at 0, 0.19, 1.45 and 4.83 mg/L vapour for 4 hours (whole body exposure). No deaths occurred. A temporary, strong narcotic effect was noted in both males and females exposed to the top concentration of 4.83 mg/L (ECHA 2018).

In a 90 day repeated dose study in SD rats (see **Repeat dose toxicity**), transient neurobehavioral changes were noted in males and females immediately after oral dosing with 400 mg/kg bw/day of the chemical. These changes included ease of handling on cage removal, posture, gait, arousal, salivation, rearing responses and aerial righting. No evidence of cumulative or persistent neurotoxicity was noted. No such changes were noted at a dose level of 125 mg/kg bw/day (ECHA 2018).

Further evidence of narcosis was presented in a developmental study in NZW rabbits. Clinical signs including decreased activity, laboured breathing, and wobbly gait were noted in both the preliminary study and the main study. Survival was low in the study. Therefore, it is difficult to ascertain whether these clinical signs were indicative of a temporary narcotic effect or signs of general toxicity due to impending death (ECHA 2018).

Systemic effects

Based on the weight of evidence of the available animal data, the chemical has the potential to cause damage to the nasal epithelium after oral and inhalation exposures. While there is no relevant information provided from acute toxicity studies, a repeat dose toxicity study (see **Repeat dose toxicity** and below) indicated that the chemical may cause damage to the nasal epithelium after only a few exposures at relatively low doses.

In a 13 week mouse inhalation study (see **Repeat dose toxicity**), dose dependent degeneration of the nasal epithelium (turbinate 2-4 only) was observed at 108 mg/m^3 after 5 exposures (incidences not provided). The incidence and severity of the degeneration present

after 5 exposures did not increase with the longer exposure. The recovery involved replacement of the olfactory epithelium with respiratory epithelium. Therefore, the damage was not considered reversible (ECHA 2018).

Furthermore, a toxicokinetic study (see **Toxicokinetics**) demonstrated that the chemical rapidly accumulates in the nasal epithelium after a receiving single oral dose of the chemical. Overall, although there is some uncertainty whether the findings to the nasal olfactory epithelium can be found after a single exposure, they are indicative of a potential acute effect. The observed effects in the olfactory epithelium warrant hazard classification of the chemical as STOT SE Category 1 that causes damage to upper respiratory tract.

Although the chemical has the potential to damage blood systems after single exposure, sufficient data are not available to determine this.

Corrosion/Irritation

Skin irritation

Two in vivo skin irritation studies in rabbits were described in the previous assessment of the chemical (NICNAS 2013). In the first study, no irritation was observed after a 4 hour application time. In the second study, the chemical was shown to be slightly irritating to rabbits following a 24 hour exposure period.

In a GLP compliant acute dermal irritation study the chemical was applied to NZW rabbits (3/group) under occlusive conditions for 3 m and 4 h, respectively (ECHA 2018). Observations were recorded at 24, 48, 72 hours, and 14 days after patch removal. The following mean scores were reported for observations at 24, 48 and 72 hours: 1.8 for erythema and 1.7 for oedema, respectively. A score of 3 for erythema and oedema was observed in at least one animal at the 48 h and 72 h timepoints. These findings were not reversible within the 14 day observation period.

Based on the persistence of the irritation effects observed, hazard classification for skin irritation is warranted (see **Hazard classifications relevant for worker health and safety** section).

Repeat dose toxicity

Based on the available data, the chemical is expected to cause serious systemic health effects in the blood system following repeated oral and inhalation exposure. Dose related effects were observed in rats and mice in both oral and inhalation studies. These effects were also noted in the developmental toxicity studies in rats and rabbits and in a two-generation toxicity study in rats. The chemical is a methaemoglobin inducer, leading to regenerative anaemia (methaemoglobinaemia). A marked increase of haemosiderosis in the spleen in combination with other changes indicated significant haemolytic anaemia following repeated exposure to the chemical. Although results from individual studies are insufficient to justify classification, the overall weight of evidence from all studies indicates effects were observed at sufficiently low doses, warranting classification (see **Hazard classifications relevant for worker health and safety** section).

Effects in both the spleen and liver were observed in rats and mice following long term, repeated exposure to the chemical. However, the toxicity observed at the level of concentrations relevant for classification was not significant. Effects on the nasal olfactory epithelium were observed in rats and in mice following repeated exposure. Although, there is

evidence that this toxicity arises as a consequence of repeated single or short term exposures (see **Acute toxicity**) and therefore classification is not warranted.

Oral

In a GLP compliant 90 day study similar to OECD TG 408, F344 rats (10/sex/dose) were administered the chemical in drinking water at doses of 0, 312, 625, 1250, 2500 or 5000 ppm equivalent to 25, 50, 100, 175, or 280 mg/kg bw/day for males and 30, 65, 120, 215 or 335 mg/kg bw/day for females.

Changes to blood parameters were observed in both males and females.

These included:

- a decrease in in red blood cell count (RBC) in males (up to 10%) at ≥100 mg/kg bw/day and in females (up to 6%) at ≥65 mg/kg bw/day
- an increase in reticulocyte counts in males (up to 78% (at ≥100 mg/kg bw/day and in females (up to 25%) at ≥30 mg/kg bw/day
- a decrease in haemoglobin levels in males (up to 5%) at ≥100 mg/kg bw/day and in females (up to 2%) at ≥65 mg/kg bw/day
- increased methaemoglobin at ≥175 mg/kg bw/day in males and ≥215 mg/kg bw/day in females
- an increase in incidence and severity of haematopoietic cell proliferation in the spleen and bone marrow at doses ≥50 and 65 mg/kg bw/day in males and females, respectively.

Percentage changes in blood parameters at each dose level were not provided.

At the higher doses (≥175 or 215 mg/kg bw/day in males and females, respectively), signs of toxicity to the liver included Kupffer cell erythrophagocytosis and haemosiderin pigmentation. There was an increase in tubular haemosiderin pigmentation in the kidney and degeneration of the nasal olfactory epithelium in both sexes. The NOAEL was reported to be 30 mg/kg bw/day based on haematological parameters in female rats at 65 mg/kg bw/day (ECHA 2018; REACH n.d.).

In a GLP compliant 90 day study similar to OECD TG 408, SD rats (10/sex/dose) were administered the chemical by gavage at 0, 40, 125 or 400 mg/kg bw/day, 5 days/week. At 40 mg/kg bw/day, effects to the blood system were observed, which included:

- a decrease in RBC count (16% in males and 19.5% in females)
- a decrease in the haematocrit (5% in males and 9.5% in females)
- increase in methaemoglobin (200% in males and 140% in females)
- increase in leukocytosis (58% in males and 49% in females)
- compensatory reticulocytosis (325% in males and 500% in females)
- Heinz body formation.

An increased spleen weight in both males and females was also reported (absolute, by 100% in males and 60% in females; relative, by 64% in males and 75% in females). No details on effects observed at doses >40 mg/kg bw/day are available. The LOAEL based on effects indicative of anaemia was determined to be 40 mg/kg bw/day (ECHA 2017; ECHA 2018).

In a non-GLP compliant 90 day study similar to OECD TG 408, SD rats (10/sex/dose) were administered the chemical by gavage at 0, 25, 75 or 225 mg/kg bw/day, 5 days/week. At

doses >25 mg/kg bw/day changes in blood parameters indicative of haemolytic anaemia and compensatory haematopoiesis in the spleen and liver were noted in both males and females. No details were given about the magnitude or severity of these changes. A NOAEL was not established (ECHA 2017; ECHA 2018).

In a GLP compliant study similar to OECD TG 407, male F344 rats (15/dose) were administered the chemical by gavage at 0, 4, 20 or 100 mg/kg bw/day mg/kg bw/day for 28 days, with a 14 day recovery period. At doses of 20 mg/kg bw/day and above, an increase in "reticulocyte ratio" was observed in males and females. An increase in platelet count and a decrease in red blood cell count, haematocrit and haemoglobin were reported in females. At 100 mg/kg bw/day, an increase in absolute and relative spleen weight, hypertrophy and haemosiderin granules in both males and females were also noted. In the liver there was an increase in haemosiderin granules in Kupffer cells and extramedullary haematopoiesis was noted in both the liver and the spleen. In the kidney there was evidence of lipofuscin like substance in tubular epithelium. No details were given about the magnitude or severity of these changes. It was stated that most changes were reversible by the end of the recovery period. The NOAEL was reported to be 4 mg/kg bw/day for the chemical, based on significant effects on blood system observed at 20 mg/kg bw/day (ECHA 2017; ECHA 2018).

In a GLP compliant two-generation study similar to OECD TG 416, SD rats (30/sex/dose) were exposed to the chemical at 0, 10, 100 or 200 mg/kg bw/day for 5 days/week for 10 weeks during pre-mating and 3 weeks during the mating period. At the highest dose a number of deaths were reported. Effects indicative of systemic blood effects were reported for all dose groups and included:

- a decrease in RBC count in the low dose F0 male group and in both sexes and both generations of the 100 and 200 mg/kg bw/day groups
- a decrease in haemoglobin in the low dose F0 male group and in both sexes and both generations of the 100 and 200 mg/kg bw/day groups
- an increase in methaemoglobin in both generations of male rats dosed with ≥100 mg/kg bw/day.

At necropsy, increases in absolute and relative spleen weight at ≥100 mg/kg bw/day were observed. Histopathology results reported extramedullary haematopoiesis and haemosiderosis of the spleen and liver in males and females of both generations at ≥10 mg/kg bw/day. An NOAEL was not established (ECHA 2017; ECHA 2018).

In a GLP compliant developmental toxicity study conducted in accordance with OECD TG 414 in pregnant SD rats (6/females/dose in a preliminary study and 25/females/dose in the main study) were administered the chemical by gavage at 0, 25, 100, 200 or 400 mg/kg bw/day (preliminary study) and 0, 60, 200 or 600 mg/kg bw/day (main study), daily from gestational day (GD) 6–GD 15.

In the preliminary study, effects to the blood were noted from the lowest dose of 25 mg/kg bw/day, which included an increase in methaemoglobin on GD 16 and 20 (6% and 4%) and an increase in reticulocyte count on GD 16 and 20 (18% and 14%). At doses ≥100 mg/kg bw/day necropsy revealed enlarged spleens. At 400 mg/kg bw/day decreased body weight, and transient wobbly gait and transient general decreased responsiveness were reported. In addition, reduced reticulocyte counts on GD 16 and 20 (81% and 36%) and reduced methaemoglobin at GD 16 and 20 (39% and 9%) were reported the highest dose.

In the main study, enlarged spleens were reported at doses ≥60 mg/kg bw/day. At 200 and 600 mg/kg bw/day transient signs of general nervous system depression (wobbly gait,

decreased responsiveness and urine stains) were reported. No effects on the blood, spleen or liver were reported in the main study.

In a GLP compliant 90 day study similar to OECD TG 408, B6C3F1 mice (10/sex/dose) were administered the chemical in their drinking water at concentrations of 0, 625, 1250, 2500, 5000 or 10000 ppm (equivalent to 110, 200, 515, 755 and 1330 mg/kg bw/day for males and 145, 340, 630, 1010 and 3170 for females). At the two highest doses, effects indicating anaemia, effects on the urinary bladder and degeneration of the nasal olfactory epithelium were observed. The NOAEL was reported to be 515 mg/kg bw/day for males and 630 mg/kg bw/day for females based on effects seen in the spleen and observed extramedullary haematopoiesis (ECHA 2017; ECHA 2018).

In a GLP compliant developmental toxicity study conducted in accordance with OECD TG 414 NZW rabbits (5 females/dose in the preliminary study and 18 females/dose in the main study) were administered the chemical by gavage at 0, 10, 20, 40 or 80 mg/kg bw/day in the preliminary study and 0, 8, 14, 24 and 40 mg/kg bw/day in the main study, daily from GD 6−18 (12 days). Significant mortality was reported at doses of 40 mg/kg bw/day and above. At 40 mg/kg bw/day 2 rabbits died on GD 10-11 (after 4-5 doses) in the preliminary study and 8 died on GD 11−24 (after ≥5 doses) in the main study.

An increased reticulocyte count and methaemoglobin were seen in the preliminary study at a dose of 10 mg/kg bw/day and in the main study at a dose of 40 mg/kg bw/day. An NOAEL was not established (ECHA 2017; ECHA 2018).

Inhalation

In GLP compliant 28 day study similar to OECD 412, F344 rats (numbers unknown/sex/dose) were exposed to vapours of the chemical at 0, 30, 101 or 340 ppm (nominal, equivalent to 22, 360 and 1440 mg/m^3), 6 h/day and 5 days/week. At the highest exposure level, decreases in haemoglobin, haematocrit, RBC count, mean corpuscular and haemoglobin concentration (10% reduction), and increases in reticulocytes, platelets and leukocytes were reported in males and females. Spleen and liver weights were also increased by 30% in both sexes. The reported NOAEC was 360 mg/m^3 based on blood effects at the 1440 mg/m^3 (ECHA 2017; ECHA 2018).

In a GLP compliant combined toxicity and carcinogenicity study similar to OECD TG 453, F344 rats (80/sex/dose in the main carcinogenicity study and 10/sex/dose sacrificed at intervals of 3, 12 and 18 months) were exposed to the chemical at vapour concentrations of 0, 15, 75 or 374 ppm (equivalent to 54, 270 and 1346 mg/m^3), 6 h/day and 5 days/week.

Changes to blood parameters were observed at all sacrifice intervals in both males and females.

These included:

- small increases in methaemoglobin, MCH, MCV, platelets and leukocytes in both sexes at 3 months interval at 1346 mg/m^3
- small decreases in haemoglobin, RBC count, MCHC in both sexes at 3 months interval at 1346 mg/m^3
- increased congestion of the spleen in males at 3 months interval at 1346 mg/ m^3, in males and females at 12 months interval at 54 mg/m^3, and in females at 18 months interval at 54 mg/m^3
- haemosiderosis and extramedullary haematopoiesis in the spleen in males at 3 months interval at 1346 mg/m^3

- haemosiderosis in the spleen in females at 270 mg/m^3 and extramedullary haematopoiesis in the spleen in males at 1346 mg/m^3 both at 12 months interval
- haemosiderosis and extramedullary haematopoiesis in the spleen in females at 18 months interval at 1346 mg/m^3.

In addition to the effects on the blood system, dose related increase in incidence and severity of degeneration of the nasal olfactory epithelium in the dorsal meatus of males and females were reported. The LOAEC based on spleen effects and effects of the olfactory epithelium in the nasal turbines was 54 mg/m^3 (ECHA 2017; ECHA 2018).

In a GLP compliant repeated dose inhalation study in CD-1 male mice, the animals were exposed to 0, 3, 10, 30 or 100 ppm (equivalent to 0, 10.8, 36, 108 or 360 mg/ m^3) of the chemical for 1, 2, 4, or 13 weeks (6 h/day, 5 days/week). There were 10 mice/group for the full exposure period; 5 mice/group for the interim periods. A recovery period of either 4 or 13 weeks was observed. A dose related incidence in the degeneration of the olfactory epithelium was observed at 108 mg/m^3 after 5 exposures (incidences not provided) and in several mice exposed to 36 mg/m^3 after 13 weeks exposures. Recovery was reported to be complete within 4 weeks following exposures at 10 ppm and nearly complete within 13 weeks after exposures at 108 and 36 mg/m^3. This recovery involved replacement of the olfactory epithelium with respiratory epithelium and therefore the damage cannot be regarded as being strictly reversible. The NOAEC for 13 weeks was 10.8 mg/m^3 (ECHA 2017, ECHA 2018).

In a GLP compliant combined 18 month repeated dose toxicity and carcinogenicity study similar to OECD TG 453 CD-1 mice (60/sex/dose in the main carcinogenicity study and 10/sex/dose at intervals of 3 and 12 months) were exposed to whole body vapours of the chemical at 0, 15, 75 or 374 ppm (equivalent to 54, 270 and 1346 mg/m^3). No treatment related effects were reported for the 3 month interval. At 12 and 18 months, effects to the liver and respiratory system were observed at the lowest dose (54 mg/m^3). In the liver there was increased haemosiderin in reticuloendothelial cells and an increase in centrilobular hypertrophy in both males and females. Granulomatous inflammation was observed in males (43% affected versus 24% in controls) and females (43% affected versus 32% in controls). There was also a slight increase in incidence of necrosis (females only). Degenerative changes and formation of replacement tissue in the olfactory epithelium in the nasal turbines was noted in both males and females. An NOAEC was not established (ECHA 2017; ECHA 2018).

In 28 day study CD-1 mice were exposed to the vapour of the chemical at 0, 30, 101 or 341 ppm (equivalent to 110, 360 and 1440 mg/m^3). Information on the number of animals per group was not provided. The only significant finding was at the top exposure level of 1440 mg/m^3, where spleen weight was increased by 30% in both males and females. No histopathology was available (ECHA 2018).

Carcinogenicity

Based on the available animal data the chemical is considered to be carcinogenic following inhalation exposure. Given the reported tumour profile and the incidence of tumours in mice and rats, the chemical is considered to have carcinogenic potential for humans, warranting hazard classification as Category 1B carcinogen.

In two separate chronic lifetime studies, performed similarly to OECD TG 453, F344 rats (50/sex/dose) and CD-1 mice (50/sex/dose) were exposed via whole body inhalation to the chemical at vapour concentrations of 0, 15, 75 or 374 ppm (corresponding to 54, 270 and

1346 mg/m^3 for 6h/day, 5days/week over 26 months and 18 months, respectively (ECHA 2018).

Both studies showed an increased incidence of liver tumours in both species at all tested exposure concentrations. There were statistically significant increases in benign (above 270 mg/m^3) and malignant tumours (1346 mg/m^3) in the livers of male rats and in malignant liver tumours in male mice (1346 mg/m^3). There were also increases in hepatocellular adenoma in female rats and mice exposed to 1346 mg/ m^3 of the chemical, but these increases were not statistically significant. There were no increased levels of malignant liver tumours seen in female rats or mice in the studies. However, there was no clear evidence in the non-neoplastic findings in the livers of the animals indicating that males might have been more sensitive than females. In the absence of a clear mechanistic explanation for the increased liver tumours, the above findings in rats and mice were considered of relevance for human health risk assessment (ECHA 2018).

Additionally, a dose related increased incidence of mammary gland fibroadenoma was observed in male rats exposed to the chemical. Statistical significance was reached at highest dose. An increase of mammary gland fibroadenomas was also observed in females, but these increases were not statistically significant. There were no non-neoplastic changes in the mammary glands of rats exposed to the chemical that might explain how these tumours arose. Uncertainty remains on whether the chemical is carcinogenic to the mammary gland of male rats and the relevance of the findings to humans (ECHA 2018).

ECHA notes that the modes of action for liver tumours in rats and mice following long term exposure by inhalation have not yet been identified and in the absence of information the tumours observed are relevant to humans (ECHA 2018). It was noted that:

- there is evidence to suggest that the chemical is not genotoxic
- it seems unlikely that blood toxicity was a factor in the hepato-carcinogenicity of the chemical
- there is limited evidence to suggest a mode of action that involved cytotoxicity for the increased incidences of liver tumours observed in rats and mice.

Results from mutagenicity or genotoxicity tests in vitro and in vivo were mostly negative (IMAP 2013, ECHA 2017).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are acute systemic effects (damage respiratory organs) and systemic long term effects (damage to the blood system and carcinogenicity).

Public risk

An MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003).

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential

adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability.

The starting points for risk characterisation are external exposure levels estimated based on modelled international use concentrations. Although some measured data were available these were not for all uses and were based on paints containing lower concentrations of the chemical. Peak concentrations have been shown to be significantly affected by concentrations (See **Human exposure**).

The critical health effects for the chemical are acute and long term systemic effects. The most likely exposure scenario is short term exposure from inhalation of paint vapour (see **Human exposure**). Based on the observed degeneration of the olfactory epithelium of the nasal cavity at 108 mg/m^3, the MOE for DIY users have been estimated as follows (Table 2):

Table 2 Margin of exposure for different products

Type of product	Inhalation mean event concentration (mg/m^3)	Margin of Exposure
Alkyd coating	223	0.5
Alkyd paint (high solid)	113	1
Alkyd paint (solvent rich)	73	1.5
Alkyd paint (aerosol)	4	27
Silicone sealant (joint)	150	0.7
Adhesive (gasketing)	3	36

The low MOEs indicates that there is a public risk that requires management.

Worker risk

Effects in the nasal epithelium have been observed following repeated exposure to the chemical in studies in animals. No human data are available.

A workplace exposure limit in Germany of 0.1 mg/m^3 has been derived from the no observed adverse effect concentration of 10.8 mg/m^3 established in a 13 week inhalation study in male CD-1-mice (see **International regulatory status**).

Limited measured exposure data indicate that worker using products containing the chemical may be exposed to levels higher than this exposure standard. It is uncertain whether this measured data reflects current formulations of products containing the chemical. Modelled and simulated exposure data indicates exposures at much higher concentrations (see **Public exposure**).

The data available, including overseas exposure standards, indicate that a workplace exposure standard may be beneficial to mitigate the risk to workers.

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