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

2-Pentanone, 4-methyl-, oxime

Assessment statement (CA09627)

5 October 2023

Final

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AICIS assessment statement (CA09627)

Chemical in this assessment

Name	CAS registry number
2-Pentanone, 4-methyl-, oxime	105-44-2

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate Application Type

AICIS received the application in a Health Focus type.

Defined scope of assessment

The chemical has been assessed:

- as imported up to 10 tonnes/annum as a component in end use coating products containing up to 0.5% concentration or in neat form for reformulation of end use coating products containing up to 0.5% concentration;
- for consumer end use products to be applied under well-ventilated settings or with adequate respiratory protections.

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured within Australia and will be imported into Australia at 10 tonnes per annum. It will be imported neat and then reformulated into surface coating products at ≤ 0.5% concentration. It will also be directly imported in finished surface coatings at ≤ 0.5% concentration. The surface coating products will be mainly for industrial or commercial use and approximately 5% of the total import volume may be available for use by do-it-yourself (DIY) users.

The assessed chemical functions as an anti-skinning agent for surface coatings. Information provided by the applicant shows that, after the coatings containing the chemical are applied to the surfaces, the chemical will be released into the air while the coatings are drying. The duration of the chemical release is expected to be approximately 8 hours until the coatings are completely dry.

The applicant stated in the submission that the introduction of the assessed chemical is intended to replace another anti-skinning chemical 2-butanone, oxime (MEKO, CAS No. 96-29-7) that is already being used in Australia.

Human health

Summary of health hazards

The identified health hazards are based on provided data for the assessed chemical and other structurally similar oximes, mainly MEKO (CAS No. 96-29-7) and 2-pentanone oxime (MPKO, CAS No. 623-40-5) (see **Supporting information** section).

The available toxicity data indicate that the assessed chemical:

- has a LD50 > 1,349 mg/kg bw in rats
- is not a skin sensitiser
- is not expected to cause specific adverse effects on fertility/sexual function and foetal development

The assessed chemical is irritating to the skin and eyes based on the observations in rabbit studies. In skin irritation studies in rabbits, irritant effects persisted to the end of the 14-day observation period. In an eye irritation study the chemical caused reversible eye irritation shown as corneal (mean score 1), iridial (mean score 1) and conjunctival effects (mean scores ≥ 2). The effects were reversible within 7 days.

The overall weight of evidence from the data available for the chemical and structurally similar oximes is sufficient to warrant hazard classification of the chemical for specific target organ toxicity with single or repeated exposure (STOT SE or RE), based on haematological effects. Significant blood effects were observed in rats after both acute and repeated oral exposure to the assessed chemical. The assessed 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 single or repeated exposure to the assessed chemical.

The assessed chemical may cause drowsiness and dizziness. Although recoverable after 48 hours, the transient narcosis effects of the chemical warrant hazard classification of STOT SE Cat 3. Behaviour changes observed in rats after acute oral exposure were indicative of neurological effects.

No inhalation toxicity data are provided for the assessed chemical. Blood effects in rats after inhalation exposure were observed from both MEKO and MPKO at doses of approximately 1,200 mg/m^3. Degeneration of the olfactory epithelium was observed with MEKO showing evidence of target organ toxicity. However, similar degeneration effects were not observed with MPKO. There is uncertainty relating to inhalation toxicity of the assessed chemical, although based on the similarity of the oximes, effects are expected to be more similar to those observed for MPKO.

The assessed chemical has concerns for carcinogenic potential based on the information on MEKO. The analogue chemical, MEKO, caused carcinogenic effects in long-term inhalation studies in both rats and mice. There is not sufficient evidence to demonstrate that the assessed chemical lacks carcinogenic potential when compared to MEKO. Although currently the assessed chemical cannot be classified as a carcinogen due to insufficient evidence, the concern remains that the assessed chemical may have similar properties as MEKO. Further specific toxicology studies may be required to investigate the carcinogenicity potential of the assessed chemical.

Hazard classifications relevant for worker health and safety

Based on the data provided by the applicant, 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 worker health and safety as follows.

Health hazards	Hazard category	Hazard statement
Skin corrosion / irritation	Skin Irrit. 2	H315: Causes skin irritation
Serious eye damage /eye irritation	Eye Irrit. 2B	H320: Causes eye irritation
Specific target organ toxicity (single exposure)	STOT SE 2	H371: May cause damage to organs (blood system)
Specific target organ toxicity (single exposure)	STOT SE 3	H336: May cause drowsiness or dizziness
Specific target organ toxicity (repeat exposure)	STOT RE 2	H373: May cause damage to organs through prolonged or repeated exposure (blood system)

Physical hazards	Hazard category	Hazard statement
Flammable liquids	Flam. Liquid 4	H227: Combustible liquid.

Summary of health risk

Public

The main route of public exposure to the chemical at up to 0.5% concentration is likely from inhalation during DIY uses. Mean event air concentrations of the assessed chemical during DIY uses have been estimated to be in the range of 7.6 to 140 mg/m^3. The estimated exposure levels are lower than those estimated for MEKO for which the assessed chemical is intended to replace. Likely health effects of the chemical include damage to the blood system and narcosis. However, due to infrequent use of the coating products in DIY settings the critical health effects for the public are expected to be acute or short-term. There are no identified risks to the public in this assessment that require management if the chemical is introduced and used in accordance with the terms of the certificate (see **Supporting information** section).

Workers

Potential exposure of workers to the assessed chemical in neat form at the reformulation sites may occur during transfer, mixing, dilution and equipment maintenance activities. Potential exposure of workers to the chemical at up to 0.5% concentration at the end use sites may occur during and after coating applications. The exposure routes may include inhalation, dermal or ocular. Given the identified long-term or acute systemic effects, local health effects and the uncertainty regarding the carcinogenic potential, the assessed chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risks to workers (see **Means for managing risk** section).

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemical is:

- Persistent (P)
- Not Bioaccumulative (not B)
- Not Toxic (not T)

Environmental hazard classification

Based on the available toxicity data, the assessed chemical is not harmful to aquatic life. No adverse effects were observed at the highest tested concentration. Therefore, the chemical does not satisfy the criteria for classification according to the GHS (UNECE 2017).

Summary of environmental risk

The assessed chemical will be introduced as a neat liquid form for reformulation into finished coatings at ≤ 0.5% concentration for use in the industrial, professional and DIY settings. The assessed chemical will also be imported as a component of the finished coatings at ≤ 0.5% concentration. These uses may result in the release of the assessed chemical to air and to sewers.

The assessed chemical is predicted to persist in the air. It has low potential to bioaccumulate and is not toxic to aquatic organisms, based on acute ecotoxicity data for two trophic levels, according to domestic threshold values.

As the assessed chemical does not meet all of the domestic PBT criteria, it is unlikely to have unpredictable long-term effects and its risk may be estimated by the risk quotient method (RQ = PEC ÷ PNEC). Based on calculated RQ values < 1 for the river and ocean compartments, the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

Public health

Information relating to safe introduction and use

- The following measures should be taken by the introducers and reformulators to minimise public exposure to the assessed chemical:
    - Labelling end use products containing the assessed chemical with safety directions to be used in well-ventilate areas or with adequate respiratory protections.

Workers

Recommendation to Safe Work Australia

- It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Hazard classifications relevant for worker 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 (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.
- The following control measures could be implemented to manage the risk arising from potential exposure to the assessed chemical during handling or reformulation activities:
    - Use of engineering controls such as
        - Enclosed and automated processes where possible
        - Adequate workplace ventilation to avoid accumulation of mists, aerosols, or vapours
    - Use of safe work practices to
        - Avoid contact with skin and eyes
        - Avoid inhalation of mists, aerosols, or vapours
    - Workers should wear the following personal protective equipment (PPE)
        - Impervious gloves
        - Protective clothing
        - Safety glasses/goggles or face mask
        - Respiratory protection where local ventilation may be inadequate

- The following control measures should be implemented to manage the risk arising from potential exposure to the assessed chemical from the end use applications:
    - Use of engineering controls such as
        - Adequate workplace ventilation to avoid accumulation of mists, aerosols, or vapours
    - Use of safe work practices to
        - Avoid contact with skin or eyes
        - Avoid inhalation of mists, aerosols, or vapours
    - Workers should wear the following PPE
        - Impervious gloves
        - Protective clothing
        - Safety glasses/goggles or face mask
        - Respiratory protection where inhalation of vapour, mist or aerosol may occur

- Spray applications should be carried out in accordance with the Safe Work Australia *Code of Practice for Spray Painting and Powder Coating* (SWA 2020a) or relevant State or Territory Code of Practice.
- The storage of the assessed chemical should be in accordance with the Safe Work Australia *Code of Practice for Managing Risks of Hazardous Chemicals in the Workplace* (SWA 2020b) or relevant State or Territory Code of Practice.
- A copy of the Safety Data Sheet (SDS) should be easily accessible to employees.

Conclusions

The conclusions of this assessment are based on the information described in this statement.

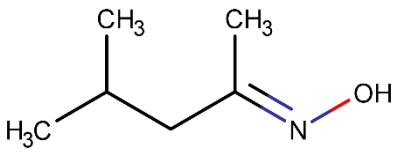
The Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the terms of the assessment certificate the human health and environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the control measures described in the statement are utilised.

Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	2-Pentanone, 4-methyl-, oxime
CAS No.	105-44-2
Synonyms	Methyl isobutyl ketoxime; MIBKO
Molecular formula	$C_6H_{13}NO$
Molecular weight (g/mol)	115.17
SMILES	ON=C(C)CC(C)C (Canonical)



Representative Structure

Chemical Description

The assessed chemical contains two geometric isomers, 2-Pentanone, 4-methyl-, oxime, (2*E*)- (CAS No. 30669-66-0), and 2-Pentanone, 4-methyl-, oxime, (2*Z*)- (CAS No. 30669-67-1), with a combined purity > 99%.

Relevant physical and chemical properties

Relevant physical and chemical properties for the assessed chemical are shown below:

Physical form	Colourless liquid
Melting point	< -27 °C
Boiling point	181.2 °C
Vapour pressure	80 Pa at 20 °C; 113 Pa at 25 °C
Density (relative)	0.899 at 20 °C
Flash point (closed cup)	79.5 °C
Water solubility	12.16 g/L at 40 °C
Ionisable in the environment?	No
log K_{ow}	1.54 at 20 °C

MPKO (CAS No. 623-40-5) and MEKO (CAS No. 96-29-7) are identified as structurally similar analogues of the assessed chemical for read-cross information purposes. The similarity indices of these analogues to the assessed chemical are 0.87 and 0.73 for MPKO and MEKO, respectively (Dice RDKit Mol, ChemTunes/ToxGPS accessed 21 July 2023). MEKO has a higher vapour pressure (1.07 kPa at 20 °C, REACH n.d.a) than MPKO (214 Pa at 20 °C, REACH n.d.b) and the assessed chemical (80 Pa at 20 °C). In addition, MEKO has a higher water solubility (100 g/L at 25 °C, REACH n.d.a) than MPKO (34.7 g/L at 19.8 °C, REACH n.d.b) and the assessed chemical (12.16 g/L at 40 °C). The relevant physical-chemical properties may affect absorption and distribution, and likely the toxicity of the chemical.

Introduction and use

The assessed chemical will not be manufactured in Australia. It will be imported into Australia as a liquid in neat form for reformulation into end use coatings or as a component in formulated ready to use coatings. The imported and reformulated end use products will contain the assessed chemical at ≤ 0.5% concentration. End use settings will be mainly for professional (commercial) use, but some of the end use products will also be available to DIY users. Both DIY users and professional workers will be instructed to apply the appropriate PPE and to assure adequate ventilation during application, in accordance with the product labels and SDS.

During reformulation the assessed chemical will be blended with other additives, solvents, and resins within enclosed and automated systems. Quality control testing will occur at the end of the blending process and then proceed to container filling via gravity feed or low pressure pumping.

Application of the end use coatings will be applied by brush, roller, or spray. For application in the industrial and commercial settings, the volume proportion for brush, roller and spray application type will be 10%, 20% and 70% respectively. The spray applications will be conducted in purpose-built spray facilities.

International regulatory status

The assessed chemical has been included in the *Assessment of regulatory needs list* by the European Chemicals Agency (ECHA) due to its carcinogenic concern (BaUA 2021). In *the Risk Management Option Analysis Conclusion Document* published by ECHA, the identified group of oximes consists of 5 structurally similar substances and their respective silane derivatives. One of the oximes, MEKO (CAS No. 96-29-7), is known to pose cancer risks and has been classified as Carc. 1B (H350 – May cause cancer) under European Union (EU) harmonised classification and labelling (CLH).

Human exposure

Workers

Reformulation

At the reformulation sites, potential dermal, ocular, and inhalation exposure of workers to the neat chemical may occur during transfer, blending, quality control testing, packaging and cleaning and maintenance of equipment. Worker exposure will be minimised through the use of engineering controls such as automated/enclosed systems, exhaust ventilation and PPE.

End use

Potential dermal, ocular, and inhalation exposure of workers to the assessed chemical in end use coatings at ≤ 0.5% concentration may occur during transfer, application, and cleaning of application equipment. Inhalation of aerosols and vapours of the assessed chemical may be also possible during spray applications. In addition, during the curing and drying stages following coating application, due to release of the chemical from the coated surfaces, inhalation of vapour of the chemical may occur to persons in close range of the application sites.

Storage

During storage there may be potential for accidental spillage of the assessed chemical in neat form or as a component in formulated end products at ≤ 0.5% concentration. Proper clean up and disposal would be required after any accidental spillage to prevent worker exposure.

Public

Potential dermal, ocular, and inhalation exposure of DIY users to the assessed chemical in end use coatings at ≤ 0.5% concentration may occur during transfer, application, drying and cleaning processes.

Inhalation exposure of DIY users to the assessed chemical at 0.5% concentration during brush/roller and spray application was estimated using the ConsExpo Web tool (version 1.1.1, RIVM). The assumed use scenarios and resulting event air concentrations that may be available for systemic inhalation exposures are summarised in the table below.

Type of product	Type of application	Application duration	Exposure duration	Inhalation mean event concentration
Aerosol alkyd paint	Spray	15 min	20 min	7.6 mg/m^3
High solid alkyd paint	Brush/roller	132 min	132 min	44 mg/m^3
Solvent rich alkyd paint	Brush/roller	132 min	132 min	39 mg/m^3
Alkyd coating	Brush/roller	60 min	60 min	140 mg/m^3

Parameters used in the estimation: Inhalation rate = 16.2 m^3/day for all scenarios; Frequency = 0.33 /year for alkyd coating, 1 /year for solvent rich alkyd paint and high solid alkyd paint, 2 /year for aerosol alkyd paint; Room volume = 34 m^3 for alkyd coating and aerosol alkyd paint, 20 m^3 for solvent rich alkyd paint and high solid alkyd paint; Ventilation rate = 1.5 /hour for alkyd coating, 0.6 /hour for solvent rich alkyd paint and high solid alkyd paint; Amount of products used = 3,000 g for alkyd coating, 1300 g solvent rich alkyd paint and high solid alkyd paint

The parameters used in the modelling are similar to those described in the Canadian screening assessment report of MEKO (Government of Canada 2010) for an adult with an average body weight of 70 kg. It is noted that inhalation exposure may be underestimated in the spray model as exposure to vapour is not considered in the spray model (RIVM 2007).

Dermal, ocular, and inhalation exposure to the assessed chemical may also occur if members of the public are allowed to enter application sites before the coatings are completely dry. If the coatings containing the assessed chemical are applied by spray, inhalation of aerosols and vapours of the chemical may also occur to persons nearby. Prolonged or repeated inhalation exposure to gradually released vapours of the chemical after the coating applications may occur to persons in the vicinity of the coated surfaces for a duration of approximately 8 hours. The assessed chemical has a calculated half-life of > 2 days in the air (persistent), with potential for longer public exposure in confined areas following the coating applications.

Information from a journal article on exposure and emission of MEKO shows that high rate of ventilation significantly reduces the concentration of the chemical in air (Chang et al. 2004). Therefore, inhalation exposure can be minimised when using the DIY products in well-ventilated areas.

Health hazard information

Acute toxicity

In a GLP compliant acute oral toxicity study (completed in 1991) similar to OECD TG 401, rats (n = 5/sex/dose) were treated with a single dose of the chemical at 0, 0.15, 0.75 and 1.50 mL/kg bw for the main groups (equivalent to 0, 135, 674, and 1349 mg/kg bw respectively based on a relative density of 0.899 g/mL). Single doses of 0.15 and 1.50 mL/kg bw were used for satellite groups. One female animal in the 1.50 ml/kg bw satellite group was found dead on day 1. No other death of animals occurred in the study, therefore the LD50 was determined to be > 1.50 mL/kg bw (equivalent to > 1349 mg/kg bw), the highest dose tested.

Reported clinical signs of toxicity included ataxia, prostration, shallow and laboured breathing, rales, decreased body temperature, lacrimation, salivation, decreased activity, reddish urine, and dark material around eyes and nose. Qualitative behaviour assessment found significant dose dependent observations over the first two days for lacrimation, pupil dilation and constriction, absence of tail and toe pinch test response and grasp response, abnormal limb and body tone, limb rotation with no resistance, abnormal body posture, spatial locomotion restriction, and absence of righting and startle response. The study authors considered the behavioural observations to be neurological effects. Exposure to the chemical also caused a transient narcosis at the mid and high dose groups which was recoverable after 48 hours of dosing. The narcotic effects observed warrant hazard classification of the assessed chemical as STOT SE 3 that may cause drowsiness or dizziness.

Some haematology parameters were affected by the treatment, showing trends of dose response. Polychromatophilia (indicating immature red blood cells) was observed in 0/5, 3/5 and 5/5 for males and 0/5, 1/5 and 3/4 for females of the control, low and high dose satellite groups, respectively. Poikilocytosis (variation in shape of erythrocytes) was observed in 1/5, 2/5 and 3/5 for males, 0/5, 2/5 and 0/4 for females of the control, low and high dose satellite groups, respectively. Anisocytosis (variation in size of erythrocytes) was observed in 1/5, 5/5 and 4/5 for males of the control, low and high dose satellite groups, respectively.

The female rats in the satellite groups also displayed significantly increased methaemoglobin levels (2.4 and 2.2 folds in the low and high dose groups respectively when compared to the control group). Statistically significantly decreased mean corpuscular haemoglobin concentration (MCHC) was observed in high dose group males (2% lower than the control group). Low dose group females also displayed statistically significant increased mean corpuscular haemoglobin (MCH) and MCHC (6% and 2% higher than the control group respectively).

Other statistically significant haematology effects observed in animals of the main study groups in comparison to the control included:

- decreased MCHC (3%) and increased mean corpuscular volume (MCV) (9%) for high dose group females
- increased reticulocyte count for high dose group males and females (92% and 68% increases respectively)

- decreased erythrocytes in mid and high dose group females (5% and 8% reduction respectively)
- decreased erythrocytes, haemoglobin concentration and haematocrit in high dose group males (12%, 9% and 8% reductions, respectively)

The haematology effects above were observed together with liver, spleen, and bone marrow changes with potential dose responses. Histopathological tissue examination indicated increased erythropoiesis in the spleen, liver, and bone marrow, and haemosiderosis and congestion in the spleen. There were statistically significant increases in the absolute and relative weight of the spleen, more pronounced in males, with relative spleen weight increased by 20% and 58% for the mid- and high- dose groups, respectively. The effects of the treatments on the blood system were evident and consistent with those observed from other structurally similar oximes (see also **Repeat dose toxicity** section), warranting hazard classification for STOT SE 2 (blood system) (see **Hazard classifications relevant for worker health and safety** section).

No information on acute dermal or inhalation toxicity of the assessed chemical was provided. Based on the above acute oral toxicity study and other acute toxicity data on structurally similar oximes (ECHA 2017; ECHA 2018), the assessed chemical is likely to cause similar narcotic and blood effects if inhaled or in contact with skin.

Corrosion/Irritation

Skin irritation

In a GLP compliant skin irritation study similar to OECD TG 404, New Zealand white rabbits (4 males and 2 females) were treated with the chemical for 24 hours under occluded conditions. Observations were recorded at designed time intervals during a 14-day period after patch removal. The mean scores were reported for observations at 24, 48 and 72 hours:

- erythema – score 2.2 for all three observations
- oedema – scores 1.3, 1.7 and 1.2 respectively

The erythema was persistent in 5 animals up to 10 days and one animal up to 14 days. The oedema was reversible in all animals within 10 days. Desquamation was also observed and persisted from days 4 to 14 in 3 rabbits. The persistent irritation effects observed warrant hazard classification Skin Irrit. 2 (see **Hazard classifications relevant for worker health and safety** section).

Eye irritation

In a GLP compliant eye irritation study similar to OECD TG 405, neat chemical was instilled into the eyes of 9 (4 males and 5 females) New Zealand white rabbits. Doses were applied at 0.1 mL and 0.01 mL into 6 and 3 animals respectively. The eyes of 3 of the 6 rabbits in the 0.1 mL treatment group were rinsed after 20 seconds of treatment and the rest of the treated eyes were unrinsed. All animals were observed at hours 1, 24, 48 and 72, and days 4 and 7.

Group 1 (0.1 mL unrinsed)

Corneal, iridial and conjunctival effects were observed. Mean scores for corneal opacity, iritis, conjunctival redness and chemosis were recorded with maximum of 1, 1, 3 and 2.67 respectively in the animals. The corneal and iridial effects were reversible within 4 days and all other effects were reversible within 7 days.

Group 2 (0.1 mL rinsed)

Corneal, iridial and conjunctival effects were observed. Mean scores for corneal opacity, iritis, conjunctival redness and chemosis were recorded with maximum of 1, 1, 3 and 2.33 respectively in the animals. All irritation effects were reversible within 4 days.

Group 3 (0.01 mL unrinsed)

Corneal, iridial and conjunctival effects were observed. Mean scores for corneal opacity, iritis, conjunctival redness and chemosis were recorded with maximum of 0, 1, 3 and 2.33 respectively in the animals. Corneal effects were reversible within 24 hours and other effects were reversible within 7 days.

Based on the reversible effects observed on the eyes, the chemical is considered as an eye irritant, warranting hazard classification of Eye Irrit. 2B (see **Hazard classifications relevant for worker health and safety** section).

Sensitisation

A GLP compliant guinea pig maximisation test (GPMT) on the chemical was conducted similar to OECD TG 406 in 15 female Hartley albino guinea pigs. One animal died during the study. Two intradermal inductions were applied at 5% concentration in Freund's complete adjuvant or propylene glycol. A topical induction was performed at 100% concentration of the chemical. The animals were challenged with 5% concentration in propylene glycol. No positive skin reactions were reported in the test. The assessed chemical is not considered to be a skin sensitiser.

Repeat dose toxicity

Oral

A journal article was provided by the applicant (Rusch et al. 2009) with test results from an unpublished 90-day repeated dose oral toxicity study showing haematological effects of the assessed chemical. Based on the information provided, the chemical is likely to have potential to cause systemic effects on the blood system following repeated oral exposure. A marked increase of haemosiderosis in the spleen in combination with other changes indicated significant haemolytic anaemia following repeated exposure to the assessed chemical. Considering together with the toxicity data from structurally similar oximes especially MEKO, hazard classification of the chemical is warranted for STOT RE 2 that may cause damage to blood system through prolonged or repeated exposure (see **Hazard classifications relevant for worker health and safety** section).

The journal article indicated that, in the repeated dose oral toxicity study in Sprague Dawley rats, the animals (15/sex/dose) were administered the chemical by gavage once daily at 0, 5, 15, and 50 mg/kg bw/day for 13 weeks with a 4-week post exposure recovery period (5/sex/dose).

Effects were seen in the blood, spleen, and kidneys.

Blood effects when compared to the controls included:

- decreased red blood cell (RBC) counts by 11% and 6% in males and females respectively at the high dose

- increased corpuscular volume (MCV) by 9% and 7% in males and females respectively at high dose
- increased white blood cells (WBC) by 27% and 40% in females at mid- and high-dose respectively, by 33% in males at high dose
- increased lymphocytes by 22% and 40% in females at mid and high doses respectively, by 34% in males at high dose
- increased thrombocytes by 11% in females at high dose
- increased corpuscular haemoglobin (MCH) by 3% and 6% in females at mid and high doses respectively, by 5% in males at high dose
- decreased haemoglobin (6%), haematocrit (7%) and MCHC (2%) in males at high dose

Increased bilirubin levels were noted in males and females at high dose. Kidney and spleen weights were elevated in the male rats at high dose. Splenic extramedullary haematopoiesis and haemosiderosis were also observed. Some degree of recovery was noted in the 4-week recovery groups. The authors of the journal article considered the no observed adverse effect level (NOAEL) was 15 mg/kg bw/day based on initial severity of the blood effects and recovery.

There is an apparent common systemic toxicity profile of the structurally similar oximes showing haemoglobin and erythrocytes as the target. Methaemoglobinaemia, anaemia and compensatory spleen activation to correct the reduced red blood cell levels have been reported (ECHA 2018; BaUA 2021).

Inhalation

No information on repeated dose inhalation toxicity of the assessed chemical was provided.

Effects on the blood system at doses of > 1,200 mg/m^3 have been observed in 28- or 90-day inhalation studies with MPKO and MEKO (ECHA 2017, REACH n.d.b).

In repeated dose toxicity studies on MEKO, in addition to effects on the blood system, degeneration of olfactory epithelium of nasal cavity was observed. Male CD-1 mice were exposed to MEKO at 0, 3, 10, 30 or 100 ppm (equivalent to 0, 11, 36, 108 or 360 mg/m^3) by inhalation for 1, 2, 4, or 13 weeks at 6 hours per day and 5 days per week. Recovery periods of either 4 or 13 weeks were noted. Degeneration of the olfactory epithelium was obvious at doses > 10 ppm (36 mg/m^3) after 5 exposures (ECHA 2017; ECHA 2018). There was some evidence that these effects were target organ toxicity rather than local irritation effects (ECHA 2018). However, similar effects on the olfactory epithelium were not observed in a 90-day inhalation study in SD rats with MPKO (nose-only with doses up to 1,240 mg/m^3). Based on the closer structural and physico-chemical similarity, effects in the nasal epithelium for the assessed chemical are expected to be more similar to those observed for MPKO.

Genotoxicity

In a GLP compliant bacterial reverse mutation assay (similar to OECD TG 471), negative results were reported for the assessed chemical in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 strains. Bacteria strains were tested with and without metabolic activation (S9 from rat liver) at concentrations of 10, 33.3, 66.7, 100, 333, 667, 1,000, 3,330, 6,670, and 10,000 µg/plate. Cytotoxicity was observed at concentrations above 6,670 µg/plate with severe lawn growth reduction at 10,000 µg/plate.

No statistically significant increases in the number of revertants were observed in any of the strains in the presence or absence of metabolic activation. The assessed chemical was not considered to be genotoxic under the conditions of the test.

The mutagenic potential of MEKO and MPKO has also been studied in series of *in vitro* and *in vivo* tests, including bacterial mutagenicity assays, mammalian cell gene mutation assays, rat chromosome aberration tests and mouse bone marrow micronucleus tests (ECHA 2018, REACH n.d.b). These studies consistently showed that the 2 structurally similar oximes were non-genotoxic.

Carcinogenicity

No specific carcinogenicity data were provided for the assessed chemical. QSAR Toolbox (version 4.2) indicates that the assessed chemical has features of C-nitroso and oxime compounds (e.g. 2-nitropropane and acetone oxime) that are interconvertible via tautomerisation. There is evidence that 2-nitropropane is directly mutagenic and carcinogenic. There is also some evidence that C-nitroso compounds may be indirectly carcinogenic via transferring the nitroso group to N-containing compound to form carcinogenic N-nitroso compounds.

Based on the information from structurally similar oximes (BaUA 2021), the potential for the assessed chemical to cause cancer also cannot be ruled out.

Long term inhalation to vapours of MEKO led to a carcinogenic effect in both rats and mice. There were statistically significant increases in benign and malignant tumours in the livers of male rats and mice at doses above 270 mg/m^3. There were also increases in hepatocellular adenoma in female rats and mice exposed to high levels of MEKO, 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, an increased frequency of mammary gland fibroadenoma was observed in male rats exposed to high level of MEKO. In females, this increase of frequency was slight compared to the controls. There were no non-neoplastic changes in the mammary glands of rats exposed to MEKO that might explain how these tumours arose. Uncertainty remains on whether MEKO is carcinogenic to the mammary gland of male rats and the relevance of the findings to human health (ECHA 2018).

However, based on the RAC opinion published by ECHA, a clear mechanism of action for carcinogenicity has not been established (ECHA 2018). It was noted that:

- there is evidence to suggest that MEKO is not genotoxic;
- it seems unlikely that blood toxicity was a factor in the hepato-carcinogenicity of MEKO;
- 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.

Further data are required to rule out the carcinogenic potential of the assessed chemical.

Reproductive and development toxicity

Based on the journal article provided (Rusch et al. 2009), the assessed chemical is not expected to cause specific adverse effects on fertility/sexual function and/or development following oral exposure.

The journal article reported that, in a non-GLP compliant one-generation reproduction toxicity study (similar to OECD TG 415), rats (Crl: CD (SD)), (n = 28/sex/dose), were administered the chemical by gavage once daily at 0, 10, 30 and 100 mg/kg bw/day for at least 70 days. The treatment started 10 weeks prior to mating for both male and female rats. Pups were directly exposed to the chemical via oral gavage from post-natal day (PND) 21 to PND 55.

Following necropsy of the parents, dose-related increase in absolute and relative organ weights for spleen, liver and kidneys (with statistically significant increases at high dose for both males and females) were reported. Increased incidences and severity of haemosiderosis were also observed in both males and females at high dose. Splenic congestion was noted. Haematology data were not evaluated in this study.

No adverse effects for the F1 pups were noted by the article authors. No changes in fertility index were reported in the treated parental groups.

For parental toxicity, a NOAEL was established by the article authors at 30 mg/kg bw/day based on histopathological findings of the spleen at the next higher dose level. For reproductive toxicity, a NOAEL was established by the article authors at 100 mg/kg bw/day based on the highest dose tested with no adverse effects observed.

Human health risk characterisation

Public

Inhalation during applying and drying of the coatings containing the assessed chemical is likely to be the main public exposure to the chemical. During DIY uses mean event air concentrations of the assessed chemical have been estimated to be in the range of 7.6 to 140 mg/m^3 (see **Human exposure** section). The estimated exposure levels are lower than those estimated for MEKO (Government of Canada 2010).

No inhalation toxicity data are provided or available for the assessed chemical. Effects to the blood system were observed from both MEKO and MPKO at doses of approximately 1200 mg/m^3. Assuming 100% inhalation absorption, the margin of exposure (MoE) for DIY users has been estimated as follows:

Type of product	Type of application	Inhalation mean event concentration	Margin of Exposure
Aerosol alkyd paint	Spray	7.6 mg/m^3	158
High solid alkyd paint	Brush/roller	44 mg/m^3	27
Solvent rich alkyd paint	Brush/roller	39 mg/m^3	31
Alkyd coating	Brush/roller	140 mg/m^3	9

The calculated MoE values indicate that some DIY users may not have adequate protection in some exposure scenarios. However, it is noted that:

- the dose levels that resulted in blood effects were reported from studies with a longer exposure duration;
- blood effects and narcotic effects are generally reversible following cessation of exposure;
- the use of adequate ventilation would reduce exposure and hence minimise the risk.

Environmental exposure

The assessed chemical will be imported into Australia as a neat liquid for reformulation into coatings or as a component of finished coatings at ≤ 0.5%. Reformulated and imported finished products will be used in industrial, professional and DIY settings. During reformulation, the assessed chemical will be transferred into a mixing vessel for blending with other additives, solvents, and resins. The reformulation processes are largely enclosed and automated. Release of the assessed chemical is only expected to occur from accidental spills during the transport, storage and product transfer stages. Accidental spills and wastes generated during the reformulation process are expected to be collected and disposed of in accordance with local government regulations.

Coatings containing the assessed chemical will be used by professional workers in industrial and non-industrial settings, and by DIY users. The coatings will be applied by spray, brush or roller. After application, the assessed chemical will evaporate from the coated surface and be released into the air. Only minimal amounts of the assessed chemical are expected to stay within the solid matrix of the coating.

During professional use, release of the chemical may occur through overspray and accidental spills. Incidental releases are expected to be collected for appropriate disposal. Wastes and residues in empty containers are expected to be collected and disposed of to landfill according to local government regulations.

For DIY use, it is conservatively assumed that up to 5% of the annual import volume of the assessed chemical may be incorrectly disposed of to sewers, down drains or to the ground due to spills, inappropriate waste disposal and washing of application equipment.

Environmental fate

Partitioning

The assessed chemical is readily water soluble (water solubility = 12.16 g/L at 40 °C). If the assessed chemical is released to surface water, a large proportion of the chemical is expected to remain in water compartment with a small proportion to partition to sediments.

The assessed chemical is highly volatile (vapour pressure = 113 Pa at 25 °C) and is not expected to partition to other compartments if directly released to air. However, the assessed chemical is not expected to significantly partition out of water into the air during STP treatment, based on SimpleTreat 3.0 model outputs (Struijs 1996).

Degradation

Based on its estimated degradation in air, the assessed chemical is persistent.

The half-life of the assessed chemical in air is calculated to be 29.842 hours (= 2.49 days), based on reactions with hydroxyl radicals (US EPA 2012; calculated using AOPWIN v1.92). The calculated half-life in air is above the domestic persistent threshold value of 2 days.

An inherent biodegradation study supplied for the assessed chemical, conducted according to OECD TG 302B, indicated 98% degradation over 28 days. However, this degradation was determined by measuring the loss of dissolved organic carbon and may have been confounded by losses of the assessed chemical due to volatility.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemical has low potential to bioaccumulate.

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficient of the assessed chemical (log K_{OW} = 1.54) is below the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC 2009).

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 5% of the total introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs 1996).

Based on the partitioning of the assessed chemical, a minimal portion of the assessed chemical will partition to air (2%) and sludge (1%). No degradation of the chemical during STP treatment has been assumed. Total removal during STP treatment is estimated to be 3%. Therefore, 97% of the volume released to STP is estimated to be released to the aquatic environment.

The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	10,000	kg/year
Proportion expected to be released to sewer	5.00%	
Annual quantity of chemical released to sewer	500	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	1.37	kg/day
Water use	200.0	L/person/day
Population of Australia	25.423	Million
Removal within STP	3%	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.26	µg/L
PEC - Ocean	0.03	µg/L

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following key measured and nominal effective concentration (EC50) values for model organisms were supplied for the assessed chemical:

Taxon	Endpoint	Method
Invertebrate	48 h EC50 > 93 mg/L	*Daphnia magna* (water flea) Immobility OECD TG 202 Static conditions Geometric mean of measured concentrations
Algae	72 h ErC50 > 100 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Nominal concentration

Chronic toxicity

The following measured 10th-percentile effective concentration (EC10) values for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Algae	72 h ErC10 ≥ 100 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Nominal concentration

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of > 186 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the most conservative endpoint value for aquatic invertebrate (> 93 mg/L). An assessment factor of 500 was applied to this endpoint as acute toxicity data were provided for two trophic levels and chronic toxicity data were provided for one tropic level (EPHC 2009).

Environmental hazard information

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Persistent (P). The assessed chemical has a calculated half-life of > 2 days in air and is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on the measured log K_{OW} value indicating a low potential to bioaccumulate, the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available acute ecotoxicity values above 1 mg/L and one available chronic ecotoxicity value above 0.1 mg/L, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

Although the assessed chemical is predicted to be persistent in the air compartment, it does not meet all three PBT criteria. It is hence unlikely to have unpredictable long-term effects (EPHC 2009). An estimate of risk may therefore be determined using the risk quotient method.

Based on the PEC and PNEC values determined above, Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of the assessed chemical to water:

Compartment	PEC	PNEC	RQ
River	0.26 µg/L	> 186 µg/L	< 0.01
Ocean	0.03 µg/L	> 186 µg/L	< 0.01

For the river and ocean compartments, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the terms of the assessment certificate, is not expected to pose a significant risk to the environment. As such, the risk from the assessed chemical can be managed, based on consideration of the environmental hazard characteristics and estimated releases.

References

BaUA (Federal Institute for Occupation Safety and Health) (2021) Group Name: MEKO, its oxime alternatives and the respective oxime-releasing silanes in paints, coatings and sealants, Risk Management Option Analysis Conclusion Document, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, accessed from ECHA website 13 September 2022.

Chang, Guo and Sparks (2004) Exposure and Emission Evaluations of Methyl Ethyl Ketoxime (MEKO) in Alkyd Paints. Indoor Air. 8. 295 - 300. DOI: 10.1111/j.1600-0668.1998.00010.x.

ECHA (European Chemicals Agency) (2017) CLH report. Proposal for Harmonised Classification and Labelling., European Chemicals Agency, accessed July 2023.

ECHA (European Chemicals Agency) (2018) Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of butanone oxime; ethyl methyl ketoxime; ethyl methyl ketone oxime, European Chemicals Agency, accessed December 2022.

EPHC (Environment Protection and Heritage Council) (2009) Environmental risk assessment guidance manual for industrial chemicals, Prepared by Chris Lee-Steere Australian Environment Agency Pty Ltd, February 2009. ISBN 978-1-921173-41-7.

Government of Canada (2010) Screening assessment for the challenge 2-butanone, oxime (butanone oxime) Chemical Abstracts Service registry number 96-29-7, Environment Canada and Health Canada, accessed 6 July 2023.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.a), Registered dossier for butanone oxime, CAS No. 96-29-7, European Chemicals Agency website, accessed 21 July 2023.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.b) Registered dossier for N-pentan-2-ylidenehydroxylamine, CAS No. 623-40-5, European Chemicals Agency website, accessed 6 July 2023.

RIVM (National Institute for Public Health and the Environment) ConsExpo Web version 1.1.1, National Institute for Public Health and the Environment, the Netherlands, accessed 6 July 2023

RIVM (National Institute for Public Health and the Environment) (2007) Paint Products Fact Sheet to Assess the Risks for the Consumer Updated version for ConsExpo 4, National Institute for Public Health and the Environment, the Netherlands, accessed 6 July 2023.

Rusch, Tveit, Waalkens-Berendsen, Wolterbeek and Armour (2009) Comparative reprotoxicity of three oximes, Drug and Chemical Toxicology, 32(4):381-394, DOI: 10.1080/01480540903154187

Struijs (1996) SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants, National Institute of Public Health and the Environment.

SWA (Safe Work Australia) (2020a) Code of Practice for Spray Painting and Powder Coating. Commonwealth of Australia.

SWA (Safe Work Australia) (2020b) Code of Practice for Managing Risks of Hazardous Chemicals in the Workplace. Commonwealth of Australia.

UNECE (United Nations Economic Commission for Europe) (2017) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition, UNECE.