Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	2-Pentanone, oxime
EC Number:	484-470-6
CAS Number:	623-40-5
Authority:	German CA
Date:	22/03/2022

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCE

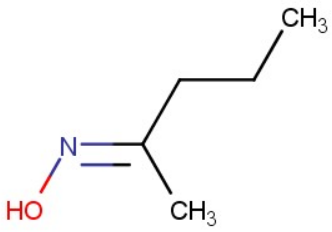
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	-
IUPAC name (public):	N-pentan-2-ylidenehydroxylamine
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	$C_5H_{11}NO$
Molecular weight or molecular weight range:	101.15 g/mol
Synonyms:	*2-PO* *2-Pentanone oxime* *MPKO* *Methyl propyl ketoxime*

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



1.2 Similar substances/grouping possibilities

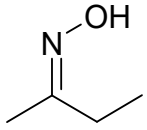
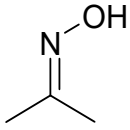
Name	butanone oxime	acetone oxime
EC No.	202-496-6	204-820-1
CAS No.	96-29-7	127-06-0
Structural formula		

Table: Substance identifiers for butanone oxime

IUPAC name (public):	Butan-2-one oxime
Index number in Annex VI of the CLP Regulation:	616-014-00-0
Molecular formula:	C_4H_9NO
Molecular weight or molecular weight range:	87.12 g/mol
Synonyms:	*2-Butanone oxime* *Butanone oxime* *Ethyl methyl ketoxime* *Ethyl methyl ketone oxime* *Ethyl methyl ketoxime* *MEKO*

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Table: Substance identifiers for acetone oxime

IUPAC name (public):	N-(propan-2-ylidene)hydroxylamine
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C_3H_7NO
Molecular weight or molecular weight range:	73.09 g/mol
Synonyms:	-

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☒ Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	☐ Compliance check
		☒ Testing proposal[1]
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restriction	☐ Annex XVII
CLH	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	☒ Dangerous substances Directive 67/548/EEC (NONS)	
	☐ Existing Substances Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment	
	☐ In relevant Annex	
Other processes/ EU legislation	☐ Other (provide further details below)	
Further details	The substance has been included in a RMOA by the German CA on "oximes of butanone, acetone, 4-methylpentan-2-one, pentan-2-one and cyclohexanone and their related silane compounds". The RMOA has been concluded in July 2021.[2]	

[1] As of May 2021, there are two TPEs for the substance ongoing according to ECHA's dissemination database: https://echa.europa.eu/de/information-on-chemicals/dossier-evaluation-status/-/dislist/substance/100.105.460

[2] https://echa.europa.eu/de/rmoa/-/dislist/details/0b0236e18447dd7d

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

The substance is not listed in Annex VI of CLP.

3.1.2 Self classification

- In the registration:

Acute Tox. 4	H302
Eye Irrit. 2	H319
STOT RE 2	H373 (blood system)
Aquatic Chronic 3	H412

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

Flam. Liq. 4	H227
Acute Tox. 4	H312
Acute Tox. 4	H332
Skin Sens. 1	H317
Eye Dam. 1	H318
Carc. 2	H351

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

There is no CLH proposal available for the substance.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[3]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
As of May 2021, there are three active registrations listed for the substance. The substance was registered as a NONS prior to the entry into force of REACH.		

***the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11): https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

4.2 Overview of uses

MPKO is used as an anti-skinning agent in coatings, varnishes, paints and sealants,used by consumers, by professional workers (widespread uses), in formulation or repacking, and at industrial sites

Table: Uses MPKO

Part 1:

☐ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☐ Closed system

Part 2:

	Use(s)
Uses as intermediate	See below.
Formulation	The substance is formulated into mixtures, i.e. liquid paints or coating products.

[3] Data based on dissemination site access on 2021-05-29

Uses at industrial sites	The substance is used in coating products. The substance has an industrial use as an intermediate in the manufacture of other substances (chemicals).
Uses by professional workers	The substance is registered for widespread use by professionals in mixtures (liquid paints), i.e. the professional application of coatings and paints. The substance is applied via non-industrial spraying, roller application or brushing and handled during mixing, blending or transfer at non-dedicated facilities.
Consumer Uses	The substance is used by consumers in coatings and paints, sealants and varnishes.
Article service life	N/A

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☐ Article 44(2)

☒ Article 45(5)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☒ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☒ C ☐ M ☐ R	☐ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[4]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☒ Other (please specify below)
Exposure/risk based concerns		
☒ Wide dispersive use	☒ Consumer use	☒ Exposure of sensitive populations
☐ Exposure of environment	☒ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☒ High (aggregated) tonnage	☐ Other (please specify below)
Human health		

[4] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

Butanone oxime (MEKO; EC: 202-496-6) is structurally similar to MPKO. It was assessed in a substance evaluation (SEv) by the DE CA in 2013. As a result of the SEv, a CLH process was initiated with the aim of harmonised classification of MEKO as Carc. 1B, H350 (among other hazard classes, e.g. STOT RE 2 (H373) for haematotoxic effects, STOT SE 1 (H370) for degenerative effects on the nasal epithelium and STOT SE 3 (H336) for narcotic effects). RAC confirmed the proposal (opinion adopted on 14. September 2018) and MEKO was added to Annex VI of the CLP Regulation in August 2020.
Acetone oxime (EC: 204-820-1), a potential substitute for and structurally very similar substance compared to MEKO, was evaluated in a SEv by the Austrian competent authority (AT CA) in 2016. The result of this evaluation was the initiation of a CLH process in 2020 to classify acetone oxime as Carc. 1B, H350, as well. Besides the proposed Carc. 1B classification, the CLH dossier also indicates that (harmonised) classification of acetone oxime is warranted among others for the hazard classes STOT RE 2, H373 (blood system) and STOT SE 3, H336 (narcotic effects), but not for nasal epithelial degeneration (STOT SE), which was confirmed for MEKO. This CLH process is currently still ongoing.

The structurally similar oxime 2-pentanone oxime (MPKO; EC: 484-470-6) was evaluated among other oximes in the RMOA by the DE CA, as there is evidence that this substance already replaces MEKO to a high degree in applications for paints, varnishes and silicone sealants (wide dispersive uses). The cumulative tonnage for the full registration is between 1,000 and 10,000 t/a. An additional NONS-registration is listed on the ECHA website, but the tonnage band for this registration is reported as confidential.

Because of its structural similarity to MEKO and acetone oxime, it is assumed that MPKO may have similar carcinogenic properties as these substances.

Database:

MEKO
For the known carcinogen MEKO several subacute and subchronic studies, respectively, are available in rats and mice. In several of these studies, in which the substance was administered orally (via gavage or in drinking water) or via inhalation (up to 400 ppm = 1440 mg/m³), MEKO elicited effects indicating haemolytic anaemia. The effects included in some cases Kupffer cell accumulation and haemosiderin pigmentation, as well as extramedullary haematopoiesis in liver, which sometimes led to increased liver weights. However, in general no histopathological effects in liver were observed in these studies, and only in one subacute gavage study in rats hepatocellular hypertrophy was reported at a high dose of 500 mg/kg bw/d. In this study, no induction of peroxisome proliferation was detected and only increased hepatic glutathione levels were noted after 14 and 28 days of exposure at ≥250 mg/kg bw/d. The effects on blood were considered to warrant harmonised classification of MEKO as STOT RE 2, H373 (blood system).
Chronic inhalation studies in rats and mice with MEKO, on the other hand, yielded an increased incidence of tumours in the liver (carcinomas and adenomas) at the highest dose. The incidence of tumours in mammary gland was also increased in male rats at the highest exposure concentration. RAC and COM considered that these effects justify classification of MEKO as Carc. 1B, H350, according to CLP. RAC concluded that "although some limited evidence that liver (cyto)toxicity may have been a factor in the liver cancer seen in rats and mice, a mode of action has not been established for butanone oxime", but indicated that "it seems unlikely that blood toxicity was a factor in the hepatocarcinogenicity of butanone oxime".

Also other hazard classes were assessed by RAC yielding in additional classification of MEKO, including (but not limited to) STOT SE 3, H 336, as narcotic effects were observed in several animal studies with different application routes immediately or shortly after administration, as well as STOT SE 1, H370 (upper respiratory tract), as damage to the olfactory epithelium was noted following both, inhalation and drinking water exposure to MEKO.

Acetone oxime

For acetone oxime, no carcinogenicity study is available. Therefore - as part of a read-across approach - information obtained from studies with MEKO was used by the AT CA to assess the carcinogenicity of acetone oxime.

Similarly as with MEKO, haematotoxicity – including extramedullary haematopoiesis in liver – was reported after repeated oral administration of acetone oxime (90 days) to rats justifying classification of acetone oxime as STOT RE 2, H373 (blood system). However and in contrast to the findings with MEKO, an early onset of liver lesions consistent with foci of cellular alteration was also observed in this subchronic study with acetone oxime. In the SEv, the AT CA considered these as precursor lesions to hepatocarcinogenesis due to their early onset and the high incidence of clear and basophilic cell foci. In addition, hepatocellular adenomas were induced in male rats after administration of acetone oxime in drinking water for 18 months in a non-guideline study, and induction of hyperplastic liver nodules (HLN) was noted in another non-guideline study in rats, administering the test compound in drinking water for 8 weeks. These findings, together with the structural and mechanistic similarities of the two substances, acetone oxime and MEKO, led to the conclusion that acetone oxime may have a carcinogenic potential as well. Therefore, acetone oxime is proposed by the AT CA to be classified as Carc. 1B, H350, and a respective CLH proposal has recently been submitted.

In addition to the proposed Carc. 1B, H350, and STOT RE 2, H373 (blood system) classification, also other hazard classes are addressed in the proposal, including (but not limited to) STOT SE 3, H 336, as transient and reversible neurological effects were reported in the acute toxicity studies with the substance itself and its analogue MEKO (see above). Contrary to the information available for MEKO, no effects of acetone oxime on the nasal epithelium were reported, that may warrant classification for the hazard class STOT SE 1/2.

MPKO

Similarly as with MEKO and acetone oxime, effects indicating substance-induced haemolytic anaemia were as well observed after repeated inhalation of MPKO for 90 days. In the same study, no histopathological effects in the liver were seen, while an increased relative liver weight was reported at the mid and high dose (≥ 150 ppm = 615 mg/m³). No effects of MPKO on the nasal epithelium were reported in the study summary.

Likewise, no liver effects or damage to the olfactory epithelium were reported after subacute inhalation exposure of rats to MPKO (14 days), but slight haematotoxicity was observed. Effects of repeated oral dosing with MPKO (gavage, "at least 5 weeks") was tested in an OECD TG 422 test design (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) in rats. Severe haemolytic anaemia, as well as a significant increase in incidence of extramedullary haematopoiesis in liver of both sexes at ≥ 50 mg/kg bw/d, but no histopathological alterations in liver (e.g. hypertrophy) were observed in this study.

Damage to the olfactory epithelium was not reported after repeated inhalation and oral exposure to MPKO and in general, no information on potential narcotic effects after exposure to the substance is available.

No further data regarding effects of MPKO after prolonged exposure are available, but it is noted that an opt-out registrant just recently submitted a testing proposal for an OECD TG 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents; date of considerations: 23 March 2021[5]).

Overall, the similarity of effect patterns observed after repeated exposure to MPKO and MEKO, respectively, suggest that MPKO may elicit the same effects as MEKO after chronic exposure However, especially as the mode of action of tumourigenesis of MEKO is currently still unknown, this assumption remains speculative. Hence, more toxicological data is considered necessary in order to be able to draw a conclusion regarding the potential of MPKO to elicit carcinogenic effects. The test proposed in a testing proposal by an opt-out registrant - oral 90-day repeated doses study is considered insufficient to clarify the carcinogenicity concern, as it cannot be assumed that neoplastic lesions or its precursors can be observed after such short exposure duration.

Repeated dose toxicity:
The structurally similar MEKO has a harmful effect on the blood and is classified accordingly as STOT RE 2, H373 (blood system). Also with the structurally similar acetone oxime, adverse effects on the blood system were observed after repeated administration. These effects justify a classification of acetone oxime in STOT RE 2, which is to be finalised in the near future.
A review of the repeated dose toxicity data of MPKO within the substance evaluation should provide information on the question whether MPKO also possesses this adverse property on the blood system and whether a corresponding classification is necessary.

Carcinogenicity:
The structurally similar substances MEKO and acetone oxime are already or will be in the near future harmonised classified as Carc. 1B. In the substance evaluation of MPKO it is to be investigated whether MPKO also has a carcinogenic property which could necessitate classification in the hazard class carcinogenicity.

Within the substance evaluation it should be investigated whether a read across to butanone oxime, acetone oxime and a use of the data on studies with repeated administration of butanone oxime is possible and can be performed.

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☐ Information ED potential	☐ Other (provide further details below)

[5] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14551/7/6/2/?documentUUID=c8b680a1-d0aa-49a3-a1c0-7969467f0b53

The substance evaluation aims to clarify the potential carcinogenic properties of the substance. An appropriate long-term test in rodents may be considered to clarify this concern. With this long-term study, the possibly adverse effect of MPKO on the blood system, i.e. the target organ toxicity after repeated administration, can then also be investigated.

5.5. Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)
If the substance is shown to act as a carcinogen and/or target organ toxicant, harmonisation of the classification (CLP hazard class: Carc.) and labelling may become necessary for MPKO and MPKO-releasing substances. Harmonised classification as Carc. 1B, H350, could potentially lead to further risk management measures (e.g. a restriction). These needs will be assessed further depending on the outcome of the data requested in the course of the substance evaluation.			