Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Acetone oxime

EC Number: 204-820-1
CAS Number: 127-06-0

CLH-O-0000007091-82-01/F

Adopted

18 March 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ACETONE OXIME

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

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Substance name: Acetone oxime
EC number: 204-820-1
CAS number: 127-06-0
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	1
Comment received				
Thank you for CLH report and FR agrees with the use of read across approach proposed for each of endpoints for which there is no data with acetone oxime.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	2
Comment received				
The DE CA appreciates the clearly and comprehensively prepared CLH dossier by the AT CA, in particular the well described and detailed read-across analysis from butanone oxime and the acetone oxime-releasing silanes to the target substance.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	3
Comment received				
The AT CA proposes classification of acetone oxime as Carc. 1B, H350, and the generic concentration limit of 0.1 %. For the assessment of the carcinogenic property of acetone				

oxime, no guideline and GLP compliant carcinogenicity study was available. In a weight-of-evidence approach, acetone oxime showed carcinogenic potential relevant for humans in a subchronic repeated dose toxicity study and two non-guideline studies, as well as carcinogenic potential in animals using a read-across from butanone oxime. Regarding butanone oxime, RAC recently concluded that the substance is a category 1B carcinogen (RAC, 2018): In rats, butanone oxime induced dose-dependently liver carcinomas in male rats (statistically significant at a high dose of 1346 mg/m³). Additionally, an increased onset of liver adenomas was observed in male and females rats, and the effect was statistically significant in males in the mid and high dose groups (≥ 270 mg/m³). Furthermore, butanone oxime induced a dose-dependent increase in incidence of fibroadenoma in the mammary gland in male rats (statistically significant at high dose). In mice, treatment of butanone oxime induced statistically significant liver carcinomas in male mice in the high dose group. An increased incidence of liver adenomas was also observed in both sexes but this effect was not statistically significant. RAC considered that butanone oxime fulfils the criteria for Category 1B carcinogen according to the CLP Regulation (RAC, 2018). Besides the plausible read-across from butanone oxime, supportive evidence for classification of acetone oxime as Carc. 1B (H351) comes from studies conducted with the substance itself. In a guideline-conform 90-day repeated dose study in SD rats, oral administration of acetone oxime induced an early and dose-dependent onset of liver lesions consistent with foci of cellular alterations (clear and basophilic cell foci), particularly in male rats (Unpublished study report, 1991c). Due to the early appearance and the high incidence, the DS considered these as precursor lesions to hepatocarcinogenesis. Additionally, increased incidence of hepatocellular adenomas was observed in male rats after administration of acetone oxime in drinking water for 18 months in a non-guideline study (Mirvish et al., 1982). In line with this, a rat liver foci model showed higher frequency of hyperplastic liver nodules (HLN) in (MRC-) Wistar rats exposed to acetone oxime via drinking water for 8 weeks (Mirvish et al., 1988). In addition, QSAR predictions gave a structural alert for carcinogenicity (QSAR Toolbox 4.3). Overall, the DE CA agrees that classification of acetone oxime as Carc. 1B, H350, is justified based on the read-across from butanone oxime (harmonised classification as Carc. 1B) and supporting data for acetone oxime itself. The DE CA further agrees that no SCL is indicated for acetone oxime.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	4
Comment received				
FR agrees with the submitter's classification proposal for carcinogenicity Carc 1B H350 using the read-across with butanone oxime. It is in line with the draft RMOA dating 2021-03-12 by Germany available on category members of oximes of butanone, acetone, 4-methyl pentan-2-one, pentan-2-one, cyclohexanone and their related silane compounds.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	Netherlands	<confidential>	Company-Manufacturer	5

Comment received

We note that the evidence for the carcinogenicity classification of the source substance Butanone oxime is made up of studies which are robust, relevant and reliable. Hence in the case of Butanone oxime the classification as Category 1B is well justified. In contrast the evidence regarding the carcinogenicity of Acetone oxime is circumstantial and is made up of several threads of evidence, each of which is individually limited i.e. i) data read-across from another substance, ii) liver nodule data, iii) unreliable carcinogenicity study data and iv) structure activity alert. Taking each point in turn:

i) The read-across of data from Butanone oxime for certain endpoints is a not unreasonable approach however by definition read-across data carries some degree of uncertainty. This uncertainty should be reflected in the classification of the target substance ie what is considered to be strong evidence for the source substance has to be considered as weaker evidence for the target. We note that there are both similarities and differences in the toxicology of simple aliphatic oximes so read-across must be used carefully (see later comments on Pentanone oxime and Cyclohexanone oxime).

ii) The liver nodule data from the 90 day study is certainly indicative of a carcinogenic concern. However in the absence of a reliable carcinogenicity study it is not certain whether or not these nodules would progress to neoplasms. The category 1B classification is based on an assumed progression to neoplasms however we have no evidence that this is the case. There are uncertainties in making the assumption that changes to liver cells such as this will lead to certain carcinogenesis. The carcinogenic process or cancer risk can be modulated by a number of factors. For instance tumorigenesis requires a tumour microenvironment which contributes to tumour growth and progression. The tumour microenvironment would need to have acquired capabilities such as changes in sustained proliferative signalling, evading growth suppressor or resisting cell death (apoptosis).

iii) The available carcinogenicity study on Acetone oxime is relatively old, has a non-standard design, only one dose was employed and is only very briefly reported. Additionally, the control groups were staggered which therefore adds an additional layer of uncertainty to the data. Taken together this makes the study unreliable. Whilst we would not want to fully dismiss the concerns raised by this study, it cannot be given the same status as the much more robust carcinogenicity data on Butanone oxime. A category 1B classification is an overly conservative interpretation of an unreliable study.

iv) The QSAR prediction from the QSAR Toolbox V3.3.5 for oximes provides no supporting mechanistic chemistry. The CLH proposal argues that the liver cell foci are pre-neoplastic and are hence indicators for carcinogenicity. So if the carcinogenicity alert is robust then it would be anticipated that all such simple aliphatic oximes should consistently demonstrate this liver pathology. However 90 day sub-chronic studies on Pentanone oxime and Cyclohexanone oxime do not demonstrate this liver pathology (source; Dissemination database). This would seem to suggest that this alert is rather weak and not simply or strongly applicable across all such related oximes.

In conclusion none of the individual lines of evidence on carcinogenicity is definitive or strong enough to justify a classification of Category 1B. Taken together the available data does indicate limited evidence of carcinogenicity and for this reason classification of Category 2 is justified. But there is insufficient strength of evidence to justify the more severe classification of Category 1B.

Dossier Submitter's Response
No reliable guideline conform carcinogenicity study with acetone oxime is available. However, several lines of evidence are available to cover this data gap and are described in the CLH report, each line has of course its own level of certainty. Please note that the strongest evidence in our WoE approach comes from read-across to the analogue substance butanone oxime. The limitations of the studies by Mirvish et al (1982) and Mirvish et al. (1988) have been clearly indicated with the assignment of the respective Klimisch scores. In addition, we have listed the QSAR alert but are far from making a general statement about other oximes based on the QSAR predictions on carcinogenicity. Nevertheless, we do not follow your argument that based on a higher level of uncertainty a less conservative approach for hazard identification should be taken. The CLP regulation and the CLP guidance specifically mention the possibility to use non-testing data for carcinogenicity. The read-across methodology as such does not qualify for assigning a lower hazard category. According to the CLP guidance, "The category will not be higher than the chemical used to read-across from, but normally may be the same. However a lower category may be applied if the read-across highlights a possible carcinogenic hazard, and thus supports a classification, but there is uncertainty as to the robustness of the read-across prediction or there is evidence, for instance from mechanistic or other studies, that the chemical may be of lower concern for carcinogenicity." We could not identify information that acetone oxime is of lower concern for carcinogenicity than the analogue substance. Therefore, we propose the same hazard category as has been agreed for the source substance butanone oxime.
RAC's response
The read-across from butanone oxime to acetone oxime, including the argumentation presented above, as well as the available data for acetone oxime *per se* have been considered by RAC and discussed in detail in the opinion document.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	6
Comment received				
FR agrees that criteria for classification as mutagen are not fulfilled for acetone oxime.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	7
Comment received				
The AT CA concluded that no classification for germ cell mutagenicity is warranted based on available negative in vitro studies with acetone oxime, as well as negative in vitro, and in vivo studies with read-across from butanone oxime and Wasox-VMAC2, respectively. The DE CA agrees that data are conclusive but not sufficient for classification.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	8
Comment received				
FR agrees with the proposed classification and ATE.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	9
Comment received				
The AT CA proposes classification of acetone oxime as Acute Tox. 4, H312, based on the LD50 value of > 1000 mg/kg bw but ≤ 2000 mg/kg bw in rabbits. The DE CA agrees with the Acute Tox. 4, H312, classification as well as with the default ATE value of 1100 mg/kg bw.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	10
Comment received				
FR agrees that the results from the study do not met CLP criteria for classification as Skin Irrit. 2. In contrast, it can be noted that the analogue substance (butanone oxime) is classified as such.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	11
Comment received				
Based on the results of a GLP compliant study similar to OECD TG 404 (only deviation: 24 h exposure instead of 4 h as recommended in the guideline), no classification for skin irritation is proposed. The DE CA agrees that data are conclusive but not sufficient for classification.				

Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	12
Comment received				
FR agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	13
Comment received				
The DE CA agrees with the Eye Dam. 1, H318, classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	14
Comment received				
FR agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	15
Comment received				
The AT CA proposes classification of acetone oxime as Skin Sens. 1B, H317, based on a positive result in a Guinea Pig Maximisation Test (OECD Guideline 406) with 40 % response after 5 % intradermal induction, although negative results were obtained in a LLNA and a mouse ear-swelling test (MEST). It is noted that similar differences in test results (particularly negative LLNA vs. positive GMPT/Buehler test) were obtained with butanone oxime which has a harmonised classification as Skin Sens. 1, H317 (here, no sub-categorisation was possible, as only high doses were tested in the positive in vivo tests preventing a firm conclusion on sub-categorisation (i.e. 1B and 1A, respectively)). Overall and in weight-of-evidence consideration, the DE CA agrees with classification of				

acetone oxime as Skin Sens. 1B, H317, according to Annex I, Part 3, Table 3.4.4 of Regulation (EC) No. 1272/2008, due to a ≥ 30 % response at > 1 % intradermal induction dose in a GPMT with acetone oxime.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	16
Comment received				
FR agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	17
Comment received				
The AT CA proposes classification of acetone oxime as STOT SE 3, H336, (May cause drowsiness or dizziness) based on available animal data with the substance: ataxia after oral administration in rats as well as hypoactivity and lethargy in rabbits and rats were observed, though the finding in rabbits may be compromised by general systemic toxicity. The mechanism of action is not known for acetone oxime. However, transient narcotic effects as shown by decreased activity, ataxia, or lethargy in laboratory animals after single exposure is of concern. It is noted that the structural similar substance butanone oxime, similarly exhibits narcotic effects in rats and rabbits after single (as well as repeated) exposure (all routes) and has a harmonised classification as STOT SE 3, H336. The DE CA agrees that classification as STOT SE 3, H336, (May cause drowsiness or dizziness) is justified for acetone oxime.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2021	France		MemberState	18
Comment received				
According to table 26, significant decrease of haemoglobin was only observed at 45 day sacrifice and not at 90 day sacrifice. In contrast, recovery animals presented a statistically significant increase of haemoglobin with tested doses. This suggests that				

effects on blood system is only transient and reversible. This can question the relevance of the proposed classification. However, we note that similar haematological findings were observed with the analogue substance, butanone oxime, leading the RAC to classify this substance as STOT RE 2.
Dossier Submitter's Response
Thank you for your comment. Please note that also effects on associated organs (spleen, liver) were observed at 45 and 90 day sacrifice and referred to as additional justification for the proposed classification as as STOT RE 2; H373.
RAC's response
RAC notes that in the CLH dossier, histopathological effects after repeated dosing are not clearly assignable to specific time points (i.e. observed at interim sacrifice, terminal/ sacrifice and/or after recovery) and with respect to severity of effects and number of affected animals. These aspects have been considered in the opinion document.

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2021	Germany		MemberState	19
Comment received				
The AT CA proposes classification of acetone oxime as STOT RE 2, H373 (May cause damage to the blood system through prolonged or repeated exposure), based on results from a GLP compliant 90-day study in SD-rats. Main adverse effects (in addition to the adaptive effects) at test doses relevant for STOT RE 2 classification (i.e. ≤ 100 mg/kg bw/d) included slight to moderate methaemoglobinaemia, reductions in haemoglobin (Hb) concentration around/above 10 % after 45 days (but not 90 days) of exposure, reductions in red blood cell counts above 10 % after 90 days of exposure, dose-dependent increases in spleen weight (females, absolute and relative), histopathological changes in spleen and liver (reported to be not reversible): liver cell foci (males, minimal; uncertainty regarding the liver cell foci being secondary to haematotoxicity, as the foci were considered pre-neoplastic and the mechanism for tumour (and thus foci) development was considered to be unlikely the haemolytic anaemia (RAC Opinion on butanone oxime (2018) and current dossier); nevertheless the relevance of this finding for STOT RE classification cannot entirely be excluded), extramedullary haematopoiesis in liver (males; minimal to slight) and spleen (both sexes; no information on severity), effect is considered adaptive, accumulation of Kupffer cells in liver (males, slight to moderate), pigment storage in spleen (significant – no information on severity). Overall, the DE CA agrees that these findings justify classification of acetone oxime as STOT RE 2, H373 (May cause damage to the blood system through prolonged or repeated exposure), although the majority of effects – particularly of histopathological effects – may be considered borderline with respect to severity. Nevertheless, the ECHA Guidance on the Application of CLP Criteria states: "the assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs" according to CLP Annex I, 3.9.1.4 (ECHA, 2017b). Moreover, these effects were observed at a dose considerably lower than the STOT RE 2 threshold (i.e. at 50 mg/kg bw/d) and more severe effects were noted at the next higher dose tested (i.e. at 250 mg/kg bw/d), e.g. spleen congestion and capsular fibrosis. In addition, initial effects indicative of (regenerative) haemolytic anaemia were already observed at a dose as low as 10 mg/kg bw/d (i.e. reduction in Hb around 10 %, reduction in haematocrit and RBC; lowest dose tested). Furthermore, the structurally similar substance butanone oxime is listed in Annex VI of the CLP Regulation as STOT RE 2,				

H373, (blood system) as well based on similar blood effects as observed with acetone oxime, supporting the classification of acetone oxime. Hence, overall the DE CA supports the classification of acetone oxime as STOT RE 2, H373 (May cause damage to the blood system through prolonged or repeated exposure), as the criteria for CLP classification as STOT RE 2 (i.e. oral (rat): 10 < C ≤ 100 mg/kg bw/d, according to Annex I, Part 3, Table 3.9.3 of Regulation (EC) No. 1272/2008) are fulfilled.
Dossier Submitter's Response
Thank you for your support. Additional remark on extramedullary haematopoiesis in spleen: It was increased in a dose-dependent manner in rats of both sexes at the 45-day interim sacrifice and the 90-day terminal sacrifice. After 45 days of exposure it is described as slight to moderate in males at 50 mg/kg bw and slight to severe in males and females at 250 mg/kg bw. After 90 days some males and females in the 50 mg/kg bw group showed slight to moderate severity. In the 250 mg/kg bw dose group the severity in females is described as moderate, in males as moderate to severe.
RAC's response
RAC thanks the DS for clarification about the time point and severity of the observed extramedullary haematopoiesis. The mentioned aspects have been considered in the opinion document.