

Committee for Risk Assessment
RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and
labelling at EU level of

**butanone oxime; ethyl methyl ketoxime;
ethyl methyl ketone oxime**

EC Number: 202-496-6

CAS Number: 96-29-7

CLH-O-0000001412-86-227/F

Adopted
14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: butanone oxime; ethyl methyl ketoxime; ethyl methyl ketone oxime

EC number: 202-496-6

CAS number: 96-29-7

Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	United States	AdvanSix Inc.	Company-Importer	1
Comment received				
Re: MEKO; 2-butanone oxime; ethyl methyl ketoxime oxime (EC: 202-496-6; CAS: 96-29-7)				
<p>Prior to October 2016, Honeywell Belgium NV, acting as lead registrant for the above-referenced substance and as the Only Representative for Honeywell International Inc., provided to ECHA an expert comment paper by Prof. Dr. W. Dekant, concerning the carcinogenicity of methyl ethyl ketoxime (butanone oxime). The conclusion drawn in the paper was consistent with and in full support of the present and existing CLP registration for MEKO:</p> <p>Acute Tox. 4*, H312, Eye Dam. 1, H318, Skin Sens. 1, H317, Carc. 2, H351</p> <p>On October 1, 2016, Honeywell spun off and transferred the ownership for its MEKO business to AdvanSix Inc. which also assumed the Lead Registrant Role. AdvanSix Inc. appointed as its Only Representative, Knoell NL BV.</p> <p>In response to the new recommendation from BAuA Germany to revise the harmonized hazard classification of MEKO, we hereby submit that BAuA's recommendation is (1) inconsistent in Dr. Dekant's paper (provided along with this submission) and with a substantial body of scientific evidence and observations, as well as with publicly available hazard profiles for MEKO. Moreover, (2) there has been no new evidence to justify changing the settled, present classification for MEKO. The recommendation from BAuA is</p>				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

based upon an alternative interpretation of the existing testing results, unsupported by evidence.

Therefore, on behalf of our co-registrants, we state our opposition to revision of the existing CLP classification for MEKO.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dr Dekant - Expert review-MEKO.pdf

Dossier Submitter's Response

The DS appreciates the registrants' comment. In the paper by Dr. Dekant, the genotoxic MOA of MEKO is questioned and he stated that the MOA regarding the induction of liver tumours is unknown. This statement is in line with the DS's view.

It is, however, to note that Dr. Dekant in his paper did not reflect on the CLP criteria on carcinogens.

The DS suggested considerations on a potential MoA in the dossier, but the CLH dossier explicitly states that the "modes of action for butanone oxime induced liver tumours in rats and mice following long-term exposure by inhalation have not yet been identified". Because no specific mode of action for butanone oxime carcinogenesis could be identified in the respective studies, other factors and mechanisms for the tumour response of butanone oxime may be also involved. Thus, based on this uncertainty, as a default the tumour responses in rats and mice have to be considered as relevant for humans.

In vivo data is available, demonstrating that MEKO significantly induces carcinomas in livers of male rats and mice ("statistically significant increases in incidence were observed at 75 ppm (270 mg/m³) and 374 ppm (1346 mg/m³) for liver adenomas in male rats and at 374 ppm (1346 mg/m³) for liver carcinomas in male rats and mice.").

Table 3.6.1 of the CLP Regulation states that classification in Cat. 1B is warranted based on "animal experiments for which there is **sufficient** evidence to demonstrate animal carcinogenicity (presumed human carcinogen)."

Moreover, the CLP Regulation further states in section 3.6.2.2.3. b):

"**sufficient** evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms **or** of an appropriate combination of benign and malignant neoplasms in

- a) two or more species of animals **or**
- b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols; **or**
- c) An increased incidence of tumours in both sexes of a species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence.
- d) A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites."

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

<p>Paragraph a and d of section 3.6.2.2.3 b) are clearly fulfilled, as significantly higher incidences of liver carcinomas were detected in male rats and mice.</p> <p>In addition, an increase in mammary gland tumours was observed in rats (also only statistically significant in males). Therefore, it can be concluded that there is clear evidence for carcinogenicity in experimental animals.</p> <p>Thus, according to the CLP Regulation the available evidence is considered sufficient to classify MEKO as Carcinogen Cat. 1 B.</p> <p>See also comment no. 11.</p>
<p>RAC's response</p> <p>RAC agrees with the assessment of Dr Dekant that a mutagenic mode of action is unlikely to account for the increased frequency of liver tumours in rats and mice.</p> <p>RAC notes that the information on the carcinogenicity of this substance is not new, but nevertheless has been tasked with assessing this against the most up to date, relevant criteria in the CLP Regulation.</p>

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2017	Germany	CD-Color GmbH & Co. KG	Company-Downstream user	2
Comment received				
<p>CD-Color GmbH is a producer of solvent based alkyd paints. More than the half of our sales depends on alkyd paints which are widely used in the building sector. Organic solvents and anti-skinning agents based on oximes are used in the processing of these products. 2-butanone oxime (MEKO = methyl ethyl ketone oxime) has been used for decades in these coating materials. Typical use concentrations of MEKO in conventional alkyd paints are between 0.3 and 0.5% in order to prevent the hardening of the paint in the container. Because of its high vapor pressure, MEKO evaporates quickly during and after application and thus does not significantly retard the drying of the lacquer. Many emission measurements show that in the phase of use, no MEKO is released from the coating material. Therefore no risk of MEKO goes out to the user of interior spaces. We remain available to provide further information.</p>				
Dossier Submitter's Response				
<p>The DS appreciates the registrants insights on the likelihood of exposure of consumers/users. Nevertheless, harmonised classification of chemicals is hazard based (reflecting the intrinsic toxicity of the chemical) and not based on risk of exposure.</p>				
RAC's response				
<p>Thank you for this information. Classification is a hazard-based reflection of the inherent properties of the substance and not how it is used.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Germany		Individual	3
Comment received				
<p>I am a toxicologist with more than 30 years of professional experience in assessing toxicology data and performing risk characterizations. I have more than 250 publications in high impact peer reviewed journals and have been appointed to a number of scientific</p>				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

advisory committees dealing with hazard and risk assessment.

A proposal to classify butanone oxime (methyl ethyl ketoxime, MEKO) (CAS 96-29-7) as a carcinogen category 1B has been submitted to ECHA. MEKO is presently classified as a Category 2 carcinogen according to CLP. MEKO causes increased incidences of liver tumors in male rats and in male mice after inhalation exposures. In male rats, a dose-response is observed for liver tumors, while dose-response is not evident in male mice. Statistically significant increases in tumor incidences were not observed in female rats or mice. In support of a classification as a category 1B, the CLH-proposal states that MEKO is a "animal carcinogen". The CLH-proposal does not justify why the present classification of MEKO as a Category 2 carcinogen is inadequate and why interpretation of the identical dataset now results in classification as a Category 1B. The CLH-proposal also overstates the results of the carcinogenicity studies regarding level of evidence for carcinogenicity and presents inconsistent conclusions on mode of action. In the section on carcinogenicity, a mutagenic mode of action for tumor initiation is discussed despite the conclusion that MEKO is not mutagenic and does not require classification "germ cell mutagenicity". Since MEKO is consistently negative in genotoxicity studies including endpoints in mammalian cell and in intact animals and the evidence for carcinogenicity in animals is more limited as stated in the CLH-proposal, a weight of evidence approach supports the conclusion that classification of MEKO as a category 2 remains appropriate.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment WD-MEKO.pdf

Dossier Submitter's Response

The DS appreciates the comment.
Dose-response is not evident in the lower dose groups in mice, because a significantly increased liver tumour incidence was only seen at the highest dose level. However, Table 3.6.1 of the CLP Regulation states, that classification in Cat. 1B can be done based on "animal experiments for which there is **sufficient** evidence to demonstrate animal carcinogenicity (presumed human carcinogen)."
Please see also comment no. 1 and no. 11.

RAC's response

Thank you for the constructive comments. RAC agrees that the available evidence points away from a genotoxic mode of action. The committee has assessed the evidence for carcinogenicity in rats (liver, mammary gland) and mice (liver) carefully. The conclusion reached after considering the findings against the relevant criteria in the CLP Regulation was that classification for carcinogenicity in category 1B is the most appropriate for butanone oxime.

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	4

Comment received

STOT RE : even if this class is open for commenting, FR would like to raise some issue.

Haematotoxicity: Based on the studies reported in table 19, the criteria for classification STOT RE seem not be reached with decrease of Hb lower than 5%. The results of the 4 first studies in table 20 are not sufficiently detailed to assess the severity of the effects cited. In contrast, effects reported at doses from 100 mg/kg bw/day in the 2 generation study are considered reflecting a significant toxicity. In this study, the effects occurring at 10 mg/kg bw/day are of borderline significance for classification purpose. However, the animals exposed can be of particular sensitivity, for example, during pregnancy and for the F1

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

generation which was exposed in utero and during post-natal development. In summary, the hematotoxicity is considered as a borderline case for classification between no classification and STOT RE2 and should be discussed at the RAC level.

Effect on olfactory epithelium: It is not clear why you consider the degeneration on the olfactory epithelium not severe enough to justify a classification as STOT RE (page 52). Moreover, could you please specify if the effects on olfactory epithelium occurred rapidly after exposure? In this case, it can be some evidence of a respiratory irritation and might warrant a classification as STOT SE.

Hepatotoxicity: Non-neoplastic liver effects are reported in the chronic/carcinogenicity study. In particular, necrosis was reported from 54 mg/m³ in mice. Could you please explain if the effects on the liver fulfil the criteria for classification as STOT RE?

We agree that no classification is warranted for mutagenicity.

We agree that no classification is warranted for reprotoxicity.

Dossier Submitter's Response

The DS appreciates the comment by the FR MSCA.

1) Haematotoxicity:

Specific results of the 4 first listed inhalation studies in table 20 of the dossier:

a) TL9 (1991), unpublished study report, confidential; Schulze and Derelanko (1993):

Effects indicative of anaemia:

m/f: ≥ 40 mg/k g bw/d: blood: \downarrow RBC count (-16%/-19.5%) and Hct (-5%/-9.5%);
 \uparrow : methaemoglobin level (+200%/+140%), leukocytosis (leukocyte counts: +58%/+49%), regenerative anaemia, compensatory reticulocytosis (reticulocyte counts: +325%/+500%), Heinz body formation, further erythrocytic morphologic changes (not further specified); spleen: \uparrow weight (abs.:+100%/+60%; rel.: +64%/+75%). LOAEL(m/f) = 40 mg/k g bw/d

b) TL1 (1977), unpublished study report, confidential; TL23 (1988), unpublished study report, confidential; TL7 (1990), unpublished study report, confidential.

No quantitative data available on the effects on the blood parameters. LOAEL for anaemia 15 mg/kg bw/d, 90-day study.

c) TL14 (1995a), unpublished study report, confidential.

No further data available

d) TL12 (1996), unpublished study report, confidential.

LOAEL for anemia 20 mg/kg bw/d/ 28-day study. No quantitative data available on the effects on the blood parameters. Severity grades on the pigment deposition (hemosiderosis) in spleen, liver and kidney not documented.

e) TL17 Effects observed in the 2-generation study at 100 mg/kg bw/d (with 10/11 week pre-mating treatment, dosing during 3 weeks of mating, and in females continued dosing during gestation and lactation (plus ca. 40 days)):

F0m + F1m: \downarrow RBC count (26/31 %), \downarrow Hb (9/14 %),

F0f + F1f: \downarrow RBC count (16/25 %), \downarrow Hb (8/11 %),

Clinical signs of toxicity: F0m: lethargy, staggering, and rooting in bedding;

F0f: weaving, tremors, and rooting in bedding; F1m: slight dehydration, audible breathing, and rooting in bedding; and F1f: laboured breathing

To the DS's view, the effects were observed in males of the F0 generation as well, and thus are not considered to be due to a particular sensitivity of the (female) animals (exposure during pregnancy or for the F1 generation in utero and during post-natal development).

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

Where available in these inhalation studies, the amount of Hb reduction did not reach the level of 20% that as a stand-alone criteria would be sufficient to warrant classification as STOT RE.

The presence of 'Marked hemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. reduction in Hb at $\geq 10\%$) in a 28-day study' was given in the CLP Guidance as an example of multiple less severe effects that could justify the classification. Hemosiderosis in spleen, liver and kidney was observed (e.g. in TL12), however information on the grading is missing.

The absolute level of methaemoglobin alone (where available) is not a robust information as the studies did not give information on whether the blood samples were gathered at the peak levels following daily exposure.

Hence, the anaemic effects may be considered as of borderline significance for classification, but missing information on severity of related toxic effect do not allow conclusion for classification of MEKO as STOT RE 2.

Only the anaemic effect (reduction in Hb $> 10\%$) in combination with the clinical signs of systemic toxicity in male rats at 100 mg/kg bw/d of the 2-generation study may support classification as STOT RE 2 (according to the criteria of the CLP Annex I, 3.9.1.4). DS appreciates a discussion at RAC.

2) Effect on olfactory epithelium

Unfortunately, acute toxicity data on nasal lesions are not available to consider whether the damage to the olfactory epithelium is also to expect after single exposure. Thus, no conclusion is possible on a classification as STOT SE with regards to acute (transient) respiratory tract irritation.

It is correct that after life-long repeated exposure to butanone oxime by inhalation effects on the olfactory epithelium of the nasal turbinates were noted in rats and mice at all concentration tested (≥ 15 ppm, equivalent to 0.054 mg/L/6h/d). In the CLH Dossier, the findings on the nasal olfactory epithelium observed in rats and mice up to the highest concentration tested of 374 ppm (1.346 mg/L/6h/d) were considered not severe enough to justify classification.

According to Newton et al. 2001 and the confidential study report, degenerative and reparative changes of the olfactory epithelium were observed primarily in the dorsal meatus. "The olfactory degeneration observed with exposure to MEKO was localized to the epithelium lining the dorsal meatus. Large areas of the olfactory epithelium lying laterally and posteriorly were unaffected." The publication reports that "olfactory epithelium was replaced by cells that ranged from squamous to cuboidal cells that resembled well differentiated respiratory epithelium that was partially ciliated". This is interpreted as degenerated olfactory cells were replaced by metaplasia and respiratory epithelium.

In a follow-up study, Newton et al. (2002) investigated and further characterised the olfactory degeneration at lower exposure levels and evaluated the time course for the development and recovery of this effect. Again, large areas of olfactory epithelium lying laterally and posteriorly as well as respiratory epithelium were reported to be unaffected. "Generally approximately 10% or less of the total olfactory tissue was affected." Moreover,

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

"50 to 90% of the animals exposed to MEKO at 30 ppm (10 times the NOEL) and a few animals exposed to 100 ppm of MEKO showed no evidence of olfactory epithelial lesions" at all.

Data indicate that incidence and severity of the degenerative changes of the olfactory epithelium depend on the air concentration of butanone oxime. Newton interpreted the findings that the "olfactory tissue damage was reversible following cessation of exposure. Recovery was complete within 4 wk following exposures at 10 ppm and nearly complete within 13 wk following exposures of 30 and 100 ppm." However, it is questionable whether a full recovery to the original olfactory epithelium was seen as it is reported that the degenerated olfactory epithelium was replaced by squamous/squamoid and/or respiratory epithelium. No incidences were reported on this 'replacement' effect.

Comparing the effects in mice at 10 ppm after 13 weeks of inhalation with the effects at 15 ppm after 18 months indicates that (at a similar low concentration) the incidences of affected animals increased with duration of the treatment. After 18 months of exposure to 15 ppm mucosal repair/replacement with squamous or respiratory was seen in 20/51 males and 23/51 (at level 4 of the nose) and higher incidences were seen in the mid and high concentrations (Newton et al., 2001, data from the confidential report). The incidences of olfactory degeneration at that time were not dose-dependent which can be expected if more or less of the original epithelium was replaced by repair tissues.

Replacement of olfactory epithelium with squamous/squamoid or respiratory epithelium

Nose Level 4:

Male mice at 0, 15, 75, 374 ppm: 0/50,20/51,43/51,47/50

Female mice 0, 15, 75, 374 ppm: 0/50,23/51,44/50,48/50

Nose Level 3:

Male mice at 0, 15, 75, 374 ppm: 0/50,21/51,44/51,47/50

Female mice 0, 15, 75, 374 ppm: 0/50,21/51,43/50,47/50

Nose Level 2:

Male mice at 0, 15, 75, 374 ppm: 0/50,23/51,43/51,43/50

Female mice 0, 15, 75, 374 ppm: 0/50,20/51,43/50,47/50

Other corroborating effects were also seen (such as Bowman gland ectasis/hyperplasia/containing eosinophilic material/debris, inflammatory cells, olfactory submucosa edema). Although severity grades were not given for the nasal effects, the extension of replaced epithelium across all levels where olfactory epithelium covers increasing fractions of the turbinates (from level 2 to 4) indicates that the effect could not be considered as a minor lesion.

The CLH report suggested no classification for STOT RE based on this comparison (Table 19):

LOAEC_{local, m/f} = 15 ppm (54 mg/m³) based on effects of the olfactory epithelium in the nasal turbinates

According to CLP: **no classification for STOT-RE**

(based on guidance value STOT-RE 2, inhalation, vapour: 3 months: ≤ 1 mg/L/6h/d;

equivalent guidance value for longer studies: 12 months $\rightarrow \leq 0.25$ mg/L/6h/d; 18 months $\rightarrow \leq 0.17$ mg/L/6h/d)

Possibly by mistake it was not realised that 15 ppm is below the guidance value for 18 months, as 15 ppm corresponds to $54 \text{ mg/m}^3 = 0.054 \text{ mg/L}$.

The rat was less sensitive than the mouse, the effects in rats occurred at concentrations above the guidance values. The observed degenerative effects in the olfactory epithelium

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

and the fact that the primary site of action was not the respiratory epithelium indicates that the mucosal degeneration is not likely due to direct irritation/cytotoxicity with a gradient of severity starting with the most severe effects in the anterior nose regions. High levels of metabolic enzymes occur in the olfactory epithelium of mammals and for most enzymes higher activities are seen in the olfactory epithelium than in the respiratory epithelium. Hypothetically P450 enzymes may be involved in the degeneration of the olfactory epithelium and differences in metabolic capacities between rat and mice may explain the species differences. This is pure assumption, no related data are available.

Degeneration of the olfactory epithelium was also observed in rats and mice exposed with the drinking water. The corresponding doses were not relevant for classification with STOT RE, but raises questions about the mode of action. Either the effect resulted from vapourised test substance that was inhaled during water uptake or could indicate a systemic effect on the olfactory epithelium.

The DS appreciates the comment from FR CA and suggests that the findings in mice after 18 months inhalation may be of primary importance to discuss the need of classification for STOT RE.

3) Hepatotoxicity

Liver effects were observed in rats and mice in the life-time studies (combined chronic toxicity/carcinogenicity studies, inhalation) in a dose-related manner. The liver changes in indicating hepatotoxicity included increased incidences of basophilic foci and vacuoles in the hepatocytes of male rats exposed at 75 ppm (270 mg/m³) and in males and females exposed at 374 ppm (1346 mg/m³). Both concentrations are above the threshold for STOT RE 2 classification. The CLH dossier says that in mice liver effects included centrilobular hypertrophy, granulomatous inflammation and necrosis at 15 ppm (54 mg/m³) and higher.

The information given in the published document of Newton is less clear, and data have been re-checked in the confidential report where the incidences also remained unclear in the written text with regards to the effects seen at 15 ppm. Clarification can only be given from the summary tables:

At the interim sacrifice after 12 months, effects were observed at all doses but also in the controls. Increased incidences of these three lesions were observed at the highest test dose and were slightly increased incidences at 75 ppm, while incidences were similar in the control and the 15 ppm treatment. After 18 months, adverse liver effects were again observed at all doses, however effects were detected in control animals as well. Incidences of all effects were markedly higher at the highest test dose, while incidences of some effects were higher at 75 ppm, depending on the sex. The only effects that were found to be increased at 15 ppm were granulomatous inflammation which was markedly increased in both sexes compared to controls (m: 43 % vs. 24 %; f: 43 % vs. 32 %) and the incidences of necrosis, which on the other hand, were only slightly increased in females, but not in males. Centrilobular hypertrophy occurred at 15 ppm at a similar rate as observed in the controls (f/m). Information on the severity is not available.

These effects are borderline effects and could meet the criteria for classification as STOT RE. The DS appreciates the proposal by FR which should be discussed in RAC.

RAC's response

RAC thanks the FR CA for the alert about possible classification for target organ toxicity and

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

takes into account the additional key information provided by the DS in relation to the STOT classification endpoint. Overall, it is concluded that the evidence for significant adverse effects at relevant exposure levels is insufficient to support classification with STOT RE.

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	Spain	Berceo Chemicals SL	Please select organisation type.	5

Comment received

MEKO (butanone oxime) has been used for over 40 years without incident. Having reviewed our own records we see no reported incidents in general use or from the general public exposure in the form of decorative & industrial paints. Checking with our end users the normal concentration in the paints supplied varies between 0.5 and 2% depending on the resin type and speed of drying required. This low level of exposure in normal use equates in most cases to most customers of less than 10MT per month and often less than 2MT even at large production sites. General consumers are exposed to such small amounts as to be close to zero as the average user in the General Public uses around 5L so 25 – 100g per exposure perhaps once per year. Currently there is no practical substitute for this product and many have tried for many years to find one. This means that the current proposal is not consistent with what everyone who uses the product sees and the evidence in reality is very different to the “studies” referred to in the CLH report (Rats & Mice therefore are not representative of actual experience in reality). Section 2.2 7-8, section 4 and p60 – 66. The key words which are misleading are everywhere in the report and not correct example is 4.9.2 “Human Information – no information is available” there are many years of information available what is clear is that it is ignored because it doesn’t match the “lab studies” and this is very wrong and brings the ECHA into disrepute.

Dossier Submitter’s Response

The DS appreciates the insights on the likelihood of exposure of consumers/users. Nevertheless, harmonised classification of chemicals is hazard based and not based on risk of exposure.

Reliable epidemiology studies of sufficient sizes, duration and quality (including robust exposure information) were not available to the DS.

RAC’s response

Thank you for this information. Harmonised classification of chemicals is hazard based and not based on risk of exposure.

There are no valid epidemiology studies to enable a reliable assessment of carcinogenic hazard based on human experience with 2-butanone oxime. In this context, no relevant information is available.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	Spain	Iberica de Componentes Quimicos SL	Company-Importer	6

Comment received

MEKO has been used for more than 40 years in the coatings and resin industry without any health concerns by the workers or indeed the general public. In general the concentration in coatings is 0.02% - 0.5% and to date no reported health concerns related to MEKO. The very low exposure levels in real use therefore give more than adequate evidence that the studies in the report are not representative. Furthermore, no other product is available with

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

<p>a comparable record of safe use as the anti skinning agent in paint for the general population to use. The effects seen in rats and mice are not seen in the human experience and when we refer to Section 2.2 7-8, section 4 and p60 - 66 inclusive and 4.10.2 page 66 in particular there is a clear mismatch and human experience completely ignored. There is no real evidence in humans and hence the correct classification is Category 2</p>
<p>Dossier Submitter's Response</p>
<p>See response to Comment no 5. In case of evidence in humans classification as carcinogen Category 1A would be relevant.</p>
<p>RAC's response</p>
<p>Thank you for this information. Harmonised classification of chemicals is hazard based and not based on risk of exposure.</p> <p>There are no valid epidemiology studies to enable a reliable assessment of carcinogenic hazard based on human experience with 2-butanone oxime. In this context, no relevant information is available.</p> <p>The animal studies do provide appropriate data to underpin the hazard assessment and classification of 2-butanone oxime for carcinogenicity.</p> <p>At the lower concentrations (< 0.1 %), some of these products containing 2-butanone oxime may not be labelled as carcinogens even into category 1B for carcinogenicity.</p>

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	United Kingdom	Sensopolis Ltd	Company-Importer	7

<p>Comment received</p>
<p>butanone oxime (MEKO) has been widely used for decades with no reported human health risks and in the vast majority of cases the concentration in the material placed on the market is 0.02% (+/- depending on individual formulation). The material has been widely used by the general public as well as industry and zero reported incidents or anything which could be traced back to butanone oxime. This is unsurprising based on the very low exposure in normal use even at production facilities and when consumers are also considered the risk is so close to zero as to be impossible to calculate. Add to this that there is no other product which performs as well or with a comparable safe use record in human health then the current proposal is clearly at odds with real life experience. The effects in Mice therefore are not seen in the human population. Section 2.2 7-8, section 4 and p60 - 66 inclusive and 4.10.2 page 66 in particular</p>
<p>Dossier Submitter's Response</p>
<p>See comment no 5. Please note that uses of Category 1 substances in mixtures at concentrations below 0.1% (if no SCL has been set) do not have to be classified and labelled.</p>
<p>RAC's response</p>
<p>Thank you for this information. Harmonised classification of chemicals is hazard based and not based on risk of exposure.</p> <p>There are no valid epidemiology studies to enable a reliable assessment of carcinogenic hazard based on human experience with 2-butanone oxime. In this context, no relevant information is available.</p> <p>The animal studies do provide appropriate data to underpin the hazard assessment and classification of 2-butanone oxime for carcinogenicity.</p>

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

At the lower concentrations (< 0.1 %), some of these products containing 2-butanone oxime may not be labelled as carcinogens even into category 1B for carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Germany	<confidential>	Company-Importer	8

Comment received

Please, see the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment COMMENTS TO PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING.pdf

Dossier Submitter's Response

In the COMMENTS TO PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING, the registrant questions the quality of the carcinogenicity test:

- 1) "Mode of dosing: not guidance mode": It is correct that inhalation experiments were performed via whole-body exposure which might lead to oral uptake due to licking and cleaning behaviour. However, results of the study cannot be neglected only based on the assumption of potential "over-exposure"
- 2) "Butanone Oxime is volatilized, forcing it in a way that should be investigated if other chemicals species are formed, and present in the air.": MEKO has a low vapour pressure indicating a low volatility. However, the DS concluded that oral exposure of MEKO is limited compared to inhalation and dermal exposure. Hence, investigating whether MEKO can elicit adverse effects via inhalation is considered necessary for a robust risk assessment and characterisation.
- 3) "Doses (extremely high). Highest dose was 1350mg/m³.": The doses used in the chronic studies were chosen based on results of preliminary range-finding studies. Based upon these results, 375 ppm was considered to be a maximum tolerated dose for the chronic study for both the rats and mice in accordance with OECD TG 451 which states "Unless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen to identify the principal target organs and toxic effects while avoiding suffering, severe toxicity, morbidity, or death".
- 4) "Mortality (very high, including controls)": As you correctly stated: The US EPA Health Effects Test Guidelines 870.4200 (US EPA, 1998b) specify that survival in any group should not fall below 50% at 15 months in the case of mice and 18 months in the case of rats, or below 25% at 18 and 24 months respectively.

Table: Percent survival after exposure for 18 months in mice and 26 months in rats

Butanone oxime Exposure (ppm)	Mice		Rats	
	Males	Females	Males	Females
0	43 %	61 %	34 %	60 %
15	57 %	51 %	37 %	58 %
75	52 %	62 %	27 %	60 %
374	48 %	65 %	43 %	76 %

In mice, the lowest survival rate after 18 months of exposure was seen in the control

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

group with 43 %, which is way above the 25 % (mice after 18 months) mentioned in the EPA Guideline. Similarly in rats, the lowest survival rate after 26 months was 27 % in the 75 ppm group. 27 % is admittedly close to the proposed minimum survival rate of 25 % (rats after 24 months), however this value is still above the proposed threshold. Thus, the results of the study are considered to be reliable.

- 5) As mentioned in the Dossier, the MoA of MEKO inducing tumours is not yet known. The substance is considered to be no genotoxicant. However, the DS does not concur with the proposed view that the occurrence of liver hemangiosarcomas is (exclusively) linked to oxidative damage subsequent to red blood cell haemolysis and iron deposition in this organ.

The DS considered a potential MoA in the dossier, however because no specific mode of action for butanone oxime carcinogenesis could be identified in the respective studies, other factors and mechanisms for the tumour response of butanone oxime may be also involved. Thus, based on this uncertainty and in accordance with the CLP Guidance, as a default the tumour responses in rats and mice have to be considered as relevant for humans.

RAC's response

Thank you for the thoughtful comments. However, RAC concurs with the response provided by the DS.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	United States	AdvanSix Inc.	Company-Importer	9

Comment received

There has been no new evidence to justify changing the settled, present classification for MEKO.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Dr Dekant - Expert review-MEKO.pdf

Dossier Submitter's Response

The TC C&L decision in 2000 was agreed as a *provisional* classification with Carc Cat 3, R40 based on the missing clarification about the MOA. Moreover, a re-assessment of the appropriateness of the harmonised classification and labelling does not require new data. In particular the transmission of the Dangerous Substance Directive to CLP Regulation needs re-evaluation of many substances. See also the response to comment no. 1 and 11.

RAC's response

RAC notes that the information on the carcinogenicity of this substance is not new, but nevertheless has been tasked with assessing this against the most up to date, relevant criteria in the CLP Regulation.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2017	Germany	CD-Color GmbH & Co. KG	Company-Downstream user	10

Comment received

The studies which led to the classification of MEKO are very old. Data from animal experiments on rats are not transferable to humans. There is no indication that the proper use of MEKO leads to health problems in humans.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

Dossier Submitter's Response
<p>The DS appreciates the comment. The studies used for classification of MEKO are considered robust and reliable irrespective of the date of origin. Moreover, as stated in the CLP Regulation (Table 3.6.1), classification in Category 1B can be done based on "animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen)." Please see also comment no. 5. The chronic/carcinogenicity studies followed the OECD Test Guidelines. The publication date in 1994 does not invalidate this information.</p>
RAC's response
<p>RAC notes that the information on the carcinogenicity of this substance is not new, but nevertheless has been tasked with assessing this against the relevant criteria.</p> <p>The animal studies do provide appropriate data to underpin the hazard assessment and classification of 2-butanone oxime for carcinogenicity. Unfortunately, no robust epidemiological data are available. The human experience alluded to does not demonstrate that butanone oxime lacks a carcinogenic hazard that is relevant to humans.</p>

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Germany		Individual	11

Comment received
<p>The CLH proposal correctly summarizes the available toxicity data on MEKO and does not propose classification for developmental toxicity and germ cell mutagenicity based on a correct interpretation of the available studies. However, in contrast to previous conclusions by EU regulatory authorities, the CLH-proposal proposes to change the classification of MEKO for carcinogenicity from the present Category 2 to Category 1B. This classification proposal is supported by the statement that "it is assumed that the reported study results for carcinogenicity do not comply with the legal classification of butanon oxime as carcinogen Category 2" without presenting and discussing the rationale why the present classification as a Category 2 carcinogen was derived and is inappropriate. The presence of liver adenoma and carcinoma in male rats and mice after inhalation of MEKO is taken as "sufficient evidence of carcinogenicity" in the CLH-proposal. A mutagenic mode of action for MEKO-tumorigenicity is discussed despite the scientifically correct conclusion in the CLH-proposal that MEKO does not need to be classified as "germ cell mutagen" (page 54ff). Weight-of-evidence considerations integrating dose-response, gender specificity of tumor induction by MEKO, absence of genotoxicity of MEKO in relevant in vitro and in vivo systems, and mode of action are not integrated to support a change in classification. In my opinion, a weight of evidence approach considering the absence of mutagenicity still supports that MEKO is a "suspected human carcinogen" and thus the present classification correctly represents the available data.</p> <p>Specific comments on effects cited as supportive for classification Inadequate discussion of the basis for the present classification of MEKO as a category 2 carcinogen in the CLH-proposal. The carcinogenicity study with MEKO and results from the genotoxicity testing of MEKO were available for the evaluation that concluded that MEKO should be classified as a Category 3 (according the former Dangerous Substances Directive; this has been taken over as Category 2 in the CLP Regulation) in 2000. Apparently, major drivers for this classification were the observations that the tumors after MEKO-inhalation occurred only in male animals and that MEKO consistently was negative in genotoxicity testing. The CLH-proposal also correctly concludes that MEKO is not genotoxic, but apparently comes to a</p>

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

different interpretation of the results of the carcinogenicity study. Good regulatory practice should only change a regulation when solid new data support a change of the present regulatory status or when new concepts regarding interpretation of hazard data have been developed. For MEKO, new data have not been generated since its classification as a Category 2 (CLP-regulation) carcinogen and guidance on the interpretation of toxicology study results has not changed. The CLH-proposal does not address the basis for the present Category 2 classification and why this is no more valid despite absence of new information. MEKO inhalation causes statistical increases in tumor incidences only in male animals. The CLH-proposal concludes that tumor induction by inhalation of MEKO in both rats and mice follows a dose-response and that liver tumors are induced in both male and female rats (page 66). This statement is not supported by the study results. A statistically increased incidence in liver adenoma only occurs in the 75 ppm and 374 ppm MEKO groups and a significant increase in the incidence of liver carcinoma in the 374 ppm group and only in male rats. Tumors in the high dose MEKO animals occurred late in life and did not affect survival. Both adenoma and carcinoma incidences in males in the 75 ppm and 375 ppm groups are also above the range of incidences from controls in inhalation studies performed by NTP in the 1980s. A comparison of control incidences recorded over the period when the study was performed is more appropriate due to changing incidences in controls due to a variety of factors. Liver adenoma incidence at 75 ppm is also outside the range of historical controls. Therefore, there is support to conclude that MEKO causes liver tumors in male rats. Since no statistically significant increases in tumor incidence in female rats was observed, a tumorigenic effects of MEKO inhalation in females is not supported. Therefore, it cannot be concluded that MEKO-inhalation causes liver tumors in both males and females; relying on statistical significance permits only the statement that MEKO inhalation induces tumors in male rats.

In mice MEKO inhalation only induced a statistically significant increase in liver carcinoma in males in the 375 ppm group, neither adenoma incidence in males nor adenoma and carcinoma incidences in female mice were significantly increased. Therefore, as in rats, only male mice are susceptible to tumor induction by MEKO inhalation and tumors in mice only occur at the highest MEKO concentration applied.

In contrast to the CLH-proposal, there is also no dose-response regarding tumor incidences in male mice nor in female rats or mice. Therefore, the CLH-proposal does not correctly state the outcome of the carcinogenicity study with MEKO since statistically significant increases in tumor incidences were not observed in female rodents. This fact considerably weakens support for the proposal to classify MEKO as a Category 1B carcinogen.

Mode of action discussed in the CLH-proposal regarding carcinogenicity is inconsistent with the conclusion that classification for germ cell mutagenicity is not required.

The CLH-proposal discusses that MEKO induced liver tumors in rodents are initiated by an interaction of a MEKO-metabolite with nucleic acids and thus a genotoxic mode-of-action. On the other side, the conclusion in the CLH-report regarding absence of a genotoxic potential for MEKO is well supported. Therefore, the discussion starting on page 67 of the CLH-proposal is confusing. Moreover, this discussion does not adequately address the inconsistencies within the postulated mode of action and absence of support for this mode of action by the available data on MEKO.

The discussed genotoxic mode of action for MEKO-induced tumors is based on mechanisms postulated for 2-nitropropane (Fiala et al., 1987; Fiala et al., 1989; George et al., 1989; Conaway et al., 1991a; Conaway et al., 1991b; Haas-Jobelius et al., 1991; Fiala et al., 1993; Fiala et al., 1995; Deng et al., 1997). As MEKO, 2-nitropropane induces tumors in rodent liver. However, both males and females are affected with higher incidences in male animals (Mirvish et al., 1982; NTP, 2002). An activation pathway involving sulfotransferases to give acetoxime sulfate was proposed based on the genotoxicity of 2-nitropropane in mammalian cells containing sulfotransferases (Sodum et al., 1993; Sodum et al., 1994; Sodum and Fiala, 1997; Kreis et al., 1998; Sodum and Fiala, 1998; Kreis et al., 2000). The

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

ultimate reactive metabolite formed from 2-nitropropane was claimed to be is hydroxylamine O-sulfate, a presumed product of the hydrolysis of acetoxime O-sulfate. However, the need for a reduction of an initial sulfate conjugate of 2-nitropropane to acetoxime O-sulfate or the chemistry of a reaction of a sulfate conjugate to give aminated DNA-bases are questionable. Many datasets are inconsistent with this mechanism since 2-nitropropane is mutagenic in bacteria without metabolic activation (Conaway et al., 1991a; Kohl et al., 1994) suggesting that other pathways of biotransformation may contribute to genotoxicity (Kohl et al., 1995; Kohl and Gescher, 1996,1997). The genotoxicity of 2-nitropropane is also increased by oxidative biotransformation possibly involving radical metabolites and acetoxime-induced DNA-damage may be mediated by metal ions (Sakano et al., 2001). Moreover, nitroreduction to an oxime apparently is not involved in the genotoxicity of 2-nitropropane (Haas-Jobelius et al., 1991)

Extrapolation of this mode of action to MEKO requires oxidation of MEKO to the corresponding 2-nitrobutane. Following this oxidation, a conjugation of 2-nitrobutane to give MEKO-sulfate should occur. Many datasets on MEKO do not support this mode of action:

- MEKO and acetoxime are not substrates for sulfotransferases (Honeywell, 2000)
- MEKO sulfate is chemically stable and has little reactivity with DNA in vitro as compared to hydroxylamine O-sulfate (Honeywell, 2000)
- Single MEKO inhalation exposures of rats does not form 8-amino-deoxyguanosine or 8-oxo-deoxyguanosine in liver DNA of male or female rats.
- While oxidation of MEKO to 2-nitrobutane has been demonstrated (Volkel et al., 1999), this is only a minor pathway of MEKO-biotransformation in rats (Burka et al., 1998). The oxidative biotransformation of MEKO is of little relevance regarding mutagenicity since, while 2-nitrobutane is mutagenic, MEKO is not (Volkel et al., 1999). Apparently, the formed 2-nitrobutane is rapidly reduced back to MEKO or rapidly further oxidized to give 2-butanone and nitric oxide (Caro et al., 2001).

The available data from MEKO genotoxicity testing correctly summarized in the CLH-proposal clearly do not support a mutagenic mode of action for liver tumor induction. It can be argued that the capacity for MEKO bioactivation by the mechanisms discussed above is not present in the in vitro systems and/or reactive metabolites formed in the liver may not reach the bone marrow. Again, this assumption is not supported by data:

- MEKO and acetoxime (Haas-Jobelius et al., 1991) do not induce DNA-damage in primary rat hepatocytes. However, primary rat hepatocytes have the metabolic capacities to bioactivate MEKO and acetoxime along the pathways postulated and 2-nitropropane induces DNA-repair in rat hepatocytes (George et al., 1989; Davies et al., 1993; Fiala et al., 1995).
- The discussed reactive sulfate intermediates formed from MEKO (Fig. 1) are stable in aqueous solution (Honeywell, 2000) and be delivered from the liver to the systemic circulation.

Therefore, the negative in vivo micronucleus test and the absence of DNA-damage in rat primary hepatocytes clearly support the conclusion that MEKO is not genotoxic as concluded the CLH-proposal. As a consequence, the discussed genotoxic mode of action has no scientific support and the absence of a mutagenic mode of action has to be considered in a weight of evidence assessment.

Conclusions

MEKO causes liver tumors in male rats and mice by a non-genotoxic mode of action. Significant increases in tumor incidence are only seen in male animals and dose-response is limited to one endpoint assessed and seen only in male rats. Integrating these conclusions on the results of the carcinogenicity testing, the sex-specific tumor induction in rodents by MEKO, and the "promoting activity" of MEKO due to the absence of genotoxicity in a weight of evidence approach support the present classification for MEKO as a category 2 carcinogen as valid.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment WD-MEKO.pdf

Dossier Submitter's Response

The DS appreciates the comment, however the DS does not concur with its conclusion.

The DS hypothesised a potential MoA in the dossier, but the CLH dossier explicitly states that the "modes of action for butanone oxime induced liver tumours in rats and mice following long-term exposure by inhalation have not yet been identified". Because no specific mode of action for butanone oxime carcinogenesis could be identified in the respective studies, other factors and mechanisms for the tumour response of butanone oxime may be also involved. Thus, based on this uncertainty, as a default the tumour responses in rats and mice have to be considered as relevant for the man.

Although the DS proposes that a genotoxic mode of action is not strongly indicated from the available information, its contribution could not be excluded. The observation that 2-nitropropane induces liver tumours in both rat sexes in comparison to MEKO which induced liver tumours only in male rats and mice does not contradict that the genotoxic action of 2-nitropropane may potentially contribute to the tumourgenicity of MEKO. Although the reason why female rodents did not show increased incidences of liver tumours is unknown, this does not totally exclude a contribution of a genotoxic MOA. However, finally the MOA is unknown.

The observation that 2-nitropropane is mutagenic in bacteria without metabolic activation suggests that the sulfotransferases pathway not be relevant for the gene mutations. In the presence of liver enzymes MEKO can be oxidised to 2-nitrobutane which (based on similarities to 2-nitropropane) should lead to a positive Ames test with S9 mix if it not rapidly reduced back or further oxidised. The reasons for the negative bacterial tests are unknown.

The observation (if a stand-alone finding) that single MEKO inhalation exposures of rats does not form 8-amino-deoxyguanosine or 8-oxo-deoxyguanosine in liver DNA of male or female rats does not exclude that DNA adducts could be produced after repeated exposures. In this case the negative outcome is supported by in-vivo data after 6 hours of inhalation that did not show DNA adducts.

With regards to other 'non-genotoxic' MOA, hepatotoxicity (such as liver cell necrosis) has been observed in mice but not in rats which showed basophilic foci. These can be considered as a preneoplastic lesion that could progress to liver tumours.

The DS does not agree on a 'promoting' effect since liver tumours were absent in the control group of rats and low in the control group of mice. The absence of strong indications of a genotoxic MOA as such does not support a 'promoting' effect or a sex-specific effect. Finally the conclusion remains that the MOA is unknown.

In addition insufficient information on the historical control incidences in mice of the same source at a relevant time window were available.

Regarding the need of new data for re-assessment, see also comment no. 9

RAC's response

RAC notes that the information on the carcinogenicity of this substance is not new, but nevertheless has been tasked with assessing this against the relevant criteria.

RAC agrees that the data from butanone oxime genotoxicity testing do not support a

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

mutagenic mode of action for liver tumour induction. The detailed analysis is appreciated. However, as indicated by the Dossier Submitter, the mode of carcinogenic action remains unknown and the tumour responses seen in rats and mice have to be considered relevant for hazard assessment. Relevance to humans cannot be discounted.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	Netherlands		MemberState	12

Comment received

- P60 (table 24), P65 and P69: The LOAEC for carcinogenicity in rats is concluded to be 15 ppm. However, no statistical changes in tumor incidence were observed at 15 ppm. Preneoplastic changes should not be used to derive a LOAEC for tumor development. Similarly, statistical significant changes in tumor incidence in mice is only observed at 374 ppm, whereas the LOAEC is concluded to be 15 ppm. The dossier submitter is asked to explain the lower LOAECs.
- Liver adenomas and carcinomas were observed in 2 species, dose-related and outside historical control values, although only with statistical significance in males. In addition, an increase in mammary gland tumours was observed in rats (also only statistically significant in males). Therefore, it can be concluded that there is clear evidence for carcinogenicity in experimental animals. Since there are no data that dispute the relevance for humans, we agree that butanone oxime should be classified as Carc. 1B
- Since no oral and dermal studies are available, and butanone oxime is readily absorbed after oral and dermal exposure (based on toxicokinetic studies), it cannot be excluded that carcinogenesis will also occur following oral and/or dermal exposure. Therefore no route specification should be included. Further, it is stated that tumour development was observed at low concentrations. Therefore, a SCL could be considered. Does this substance fulfil the criteria for a SCL?

Dossier Submitter's Response

The DS appreciates the comments by the NL MSCA.

- 1) The CLP Guidance (section 3.6.2.3.2.) states that "benign tumours may also be of significant concern and the strength of evidence for carcinogenicity that they provide should be considered using expert judgement. For instance, some benign tumours may have the potential to progress to malignant tumours and therefore any indication that the observed tumours have the potential to progress to malignancy may increase the level of concern".
As a clear dose-response relationship was observed regarding incidences of liver tumours (carcinomas and adenomas), the lowest dose at which adverse tumour development in liver was observed (15 ppm) is considered the LOAEC, as the incidence was (although not statistically significant) different from internal controls (rats: 0 % vs. 4 %; mice: 12 % vs. 26 %). Increased incidences of adenoma development compared to the historical control data (3.9 % vs. 0.33% for male rats) was observed at 15 ppm. The observed adenoma development was considered treatment-related at 15 ppm.
- 2) The DS appreciates the supporting comment by the NL MSCA.
- 3) The DS appreciates the supporting comment by the NL MSCA. The T25 value based on the exposure concentration of 75 ppm (270 mg/m³; significant increase in tumour development in rats, ~ 10 %) is 492 mg/m³ (6h/day) which corresponds to about 108.3 mg/kg bw/day according to the CLP-Guidance. According to the EC guidance, MEKO is thus a carcinogen of low potency, as the T25 value is > 100 mg/kg bw/day. According to the EC Guideline (Guideline for setting specific concentration limits for carcinogens in Annex I of Directive 67/548/EEC), the low potency group could justify

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

a SCL of 1.0%. The SCL setting was not addressed in the dossier. The DS agrees that the SCL of 1.0% is worth to be discussed at RAC.
RAC's response
RAC agrees with the perspective offered about the potential relevance of the tumour findings in rats and mice. Having made an independent assessment of T25, RAC has concluded that inclusion of a specific concentration limit for carcinogenicity would not be appropriate (see Opinion Document). Butanone oxime meets the criteria for a "medium potency" carcinogen.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Austria		MemberState	13
Comment received				
The dossier submitter compiled in the CLH report sufficient evidence on the endpoint carcinogenicity and therefore we support the proposed change of the current harmonized classification to Carc. 1B, H350.				
Dossier Submitter's Response				
The DS appreciates the supporting comment by the Austrian MSCA.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	14
Comment received				
We agree with the proposed classification based on the liver tumours in male mice and rats and on fibroadenomas in mammary gland in male rats.				
<p>Since the effects only occurred in one sex, have you made some hypothesis on a mode of action that can explain why males are more sensitive to carcinogenicity of the substance? In particular, the postulated mode of action for the liver effects is related to biotransformation to nitronate. However, it is stated in page 68 that there is no sex difference in the microsomal oxidation.</p> <p>Significant non-neoplastic effects were reported in the studies, including degeneration of the olfactory epithelium and effects in the liver, from concentrations lower than those inducing tumours. In particular, necrosis of the liver are reported from 54 mg/m³ in the mice. Necrosis could lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses (see CLP guidance page 385). Could you please give further arguments to justify that the MTD is not exceeded?</p>				
Dossier Submitter's Response				
The DS appreciates the supporting comment by the FR MSCA.				
<p>Because no species-specific mode of action for butanone oxime carcinogenesis could be identified in the respective studies, other factors and mechanisms for the tumour response of butanone oxime may be also involved. We currently have no hypothesis regarding the sex difference. As an idea, gender disparity regarding the development of chemical induced liver carcinomas was seen in mice in previous studies (e.g. Naugler et al. 2007), indicating that estrogen-mediated effects might reduce liver cancer risk in female mice. However, this is pure speculation and its relevance to MEKO unknown.</p>				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

For further considerations regarding the potential MoA of MEKO inducing tumour development please see also comment no. 11.

The CLP Guidance states "The MTD is the highest dose of the test agent during the bioassay that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity. Data obtained from a sub-chronic or other repeated dose toxicity study are used as the basis for determining the MTD". The authors of the study performed 2 range-finding studies preceding the main study to identify the MTD and mortality in the highest concentration treatment was shown to be 5 % lower in mice and 9 % lower in rats after the exposure duration. Moreover, if the MTD was too high, local incidences such as adverse site-of-contact effects would have been expected. However, the authors of the study did not detect any adverse findings in the lungs. In addition, an increase in mammary gland tumours was observed in rats, whereas no necrosis was found in this tissue. Therefore, it can be concluded that there is clear evidence for carcinogenicity in experimental animals at test concentration which did not induce severe nonspecific toxicity exceeding the MTD.

For further details on study results regarding effects on the olfactory epithelium please see also comment no. 4.

RAC's response

RAC appreciates the questions posed by the FR MSCA and the points provided in response by the Dossier Submitter to clarify their rationale for proposing a category 1B classification for carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	Spain	Berceo Chemicals SL	Please select organisation type.	15

Comment received

The role of MEKO in the development of tumours in mice and rats have never been observed in the humans. The general public and industry have used this chemical in almost every country in the world for more than 40 years in a many applications including as decorative paint in almost every house. This extremely wide pool of human information has been completely ignored by the report and so casts enormous doubt on any findings as statistically there should be some human evidence and there is none. This means that there is no justification for the proposed classification of Cat1 as the report says "There are no epidemiological studies available which demonstrate that butanone oxime induced cancer in humans" (4.10.4 page 66) Section 2.2 p7-8. and p60 – 66. As there is no supporting evidence based on the wide human exposure over such a long period of time the real life experience should prevail over the rather contrived lab tests. This is the primary evidence for classification and on that basis the carcinogenic potential is so small as to be not relevant – as with titanium dioxide another material where human experience is being ignored and again referring to page 66 "There are no epidemiological studies available which demonstrate that butanone oxime induced cancer in humans." Page 69 also demonstrated poor logic with the comment "There is no indication in the available investigations that the determined carcinogenicity in rats and mice has no relevance to humans." – whereas the contrary is true. The wide real life data shows that there is no evidence to support the classification of carcinogenic in any form based on real human experience so we should at worst case scenario base the classification on criteria b "there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies;" However, even this is dubious since there is no evidence of human tumour formation – so in reality it cannot be classified as even a suspected carcinogen – where is the real life evidence of even 1 case? This over classification really brings the work of the

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

ECHA into question if we cant trust any of the work being done to reflect reality
Dossier Submitter's Response
The DS appreciates the comments. However, reliable epidemiology studies of sufficient sizes, duration and quality (including robust exposure information) were not available to the DS. Please also see comments 1, 3, 5 and 6.
RAC's response
RAC observes that the Dossier Submitter addressed the carcinogenicity endpoint in accordance with established regulatory practice under CLP. The animal studies were sufficiently well conducted for the results to be of relevance for the hazard assessment required to address how butanone oxime should be classified. Unfortunately, no robust epidemiological data are available. The human experience alluded to does not demonstrate that butanone oxime that butanone oxime lacks a carcinogenic hazard that is relevant to humans.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	Spain	Iberica de Componentes Quimicos SL	Company-Importer	16

Comment received
Tumours are not and never have been seen in the human population despite its extensive and wide use by the General Public over more than 40 years in all types of alkyd coatings. It is clear that the report does not represent this adequately and ignores these facts showing only the limited evidence in mice and rats, the report admits there is no evidence in the real use situations. The proposed classification should therefore be downgraded back to Category 2. Section 2.2 p7-8. and p60 - 66 inclusive, provide no link to the human experience and hence category 2 (suspected) is the most that can be justified from the report. It is my view that until these real life experiences are considered the evidence submitted is not conclusive.
Dossier Submitter's Response
The DS appreciates comments. However, reliable epidemiology studies of sufficient sizes, duration and quality (including robust exposure information) were not available to the DS. Please also see comments 3, 5 and 6.
RAC's response
RAC shares the same perspective as the Dossier Submitter about the value of the human data. Please refer to the RAC Opinion for an assessment of how butanone oxime should be classified for this endpoint.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	United Kingdom	Sensopolis Ltd	Company-Importer	17

Comment received
The effects in mice and rats and the development of tumours, are not and never have been seen in the human population based on several decades of use in a wide range of environments from production to consumer use in domestic paint supplies. Hence it is clear that whilst the report shows evidence in mice there is no substantiating evidence in the real life situation. There is no justification for the proposed classification. Section 2.2 p7-8. and p60 - 66 inclusive, no evidence in humans ever found, no supporting evidence in the

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

community, wide disparity between experimental data and real life experience. Therefore the human health experience should override the laboratory tests as the primary evidence for carcinogenic potential. To quote page 66 "There are no epidemiological studies available which demonstrate that butanone oxime induced cancer in humans." Page 69 flawed comment "There is no indication in the available investigations that the determined carcinogenicity in rats and mice has no relevance to humans." - on the contrary there is no evidence to support that it is relevant to humans in the form of human experience. Flawed conclusion page 71 "In conclusion, the available data for carcinogenicity of butanone oxime does not comply with the legal classification of butanone oxime as carcinogen Category 2. Butanone oxime rather fulfils the criteria for classification and labelling as Category 1B carcinogen, H350 according to CLP." based on criteria b "there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies;" Hence at worst Category 2 and even there, there is NO EVIDENCE OF HUMAN TUMOUR FORMATION. So even this classification is over classified.
Dossier Submitter's Response
The DS appreciates comments. However, reliable epidemiology studies of sufficient sizes, duration and quality (including robust exposure information) were not available to the DS. Please also see comments 3, 5 and 6.
RAC's response
RAC shares the same perspective as the Dossier Submitter about the value of the human data. Please refer to the RAC Opinion for an assessment of how butanone oxime should be classified for this endpoint.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Germany	<confidential>	Company-Importer	18
Comment received				
Please see the full document, attached. Conclusions are: 1. There are no known non-genotoxics carcinogens to be liver tumorigenic- it is well described that this is a typical false positive. 2. Treatment-related effects are seen only at toxic doses, concomitant with haemolitical anemia. Those are also concordant with the specie-specificity for anemia and the time to disappear tumourogenic effects. 3. In absence of toxicity excess, no tumours are seen in any specie or gender. 4. CLP principles are not met; for category 1B carcinogen : Taking into account all available data on butanone oxime, we believe that no additional classification on carcinogenicity hazard is justified neither from the CLP principles nor scientifically on the light of the available data. ECHA note – An attachment was submitted with the comment above. Refer to public attachment COMMENTS TO PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING.pdf				
Dossier Submitter's Response				
The DS appreciates the comments. There is no evidence for species-specificity of the				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

<p>haemolytic effects.</p> <p>Please see comment no. 1 and 8 for details.</p>
<p>RAC's response</p> <p>Liver tumours are seen in rats and mice exposed to butanone oxime. RAC understands that tumour findings such as these in rats and mice, occurring under controlled laboratory conditions, may not always be relevant to humans. However, in the case of butanone oxime, the basis for the increased tumour findings is not known and their relevance for human hazard assessment cannot be discounted.</p>

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Austria		MemberState	19
Comment received				
<p>We support the dossiers submitters proposal for oral and dermal acute toxicity, Acute Tox. 3, H301 and Acute Tox. 4,H312 based on experimental evidence in rabbits. Based on the acute oral and repeated toxicity studies the rabbit appears to be more susceptible to acute toxic effects of butanone oxime. Butanone oxime clearly displayed adverse ocular effects therefore classification with Eye Cat 1, H318 is warranted.</p>				
Dossier Submitter's Response				
<p>The DS appreciates the supporting comment by the Austrian MSCA.</p>				
RAC's response				
<p>Noted.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	20
Comment received				
<p>Oral route: We question on the adequacy to use results from Derelanko et al (2003) study for classification as acute toxicity. Indeed, the lowest LD50 obtained from these preliminary and main prenatal studies compared to the acute studies in rats can be due to a higher sensitivity of rabbits but also a higher sensitivity of pregnant animals. In addition, it should be noted that rabbit is not one of the common species recommended for acute oral toxicity. Furthermore, mortalities occurred not only after a single exposure but after exposure lasting 2 to 5 days. Thus, repeated administration may also explain that mortalities occurred at lower doses in this study. Overall, we consider that a classification for acute oral toxicity is warranted as category 4 based on the TL5 (1982).</p> <p>Inhalation: We agree that no classification is warranted.</p> <p>Dermal route: We agree with the proposed classification as category 4.</p>				
Dossier Submitter's Response				
<p>The DS appreciates the comment by the FR MSCA.</p> <p>Oral route: Admittedly, the CLP Guidance states that the "preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat". However, it also states that when "experimental data for acute toxicity are available in several animal species, scientific judgement shall be used in selecting the most appropriate LD50 value from among valid,</p>				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

well-performed tests." Moreover, it states: "In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested."

It cannot be excluded that the rabbit is the most sensitive species regarding acute toxicity of MEKO irrespective of the reproductive state, thus, this study has to be considered relevant. Moreover, first deaths (2/5 females) occurred extremely fast, less than 48 hours after two dosages (cumulative dose of 160 mg/kg bw) and it cannot be excluded that a single dosing would have resulted in delayed mortality as well. Accordingly, the LD50 value for butanone oxime was not calculated but roughly estimated as being ≤ 160 mg/kg bw (2 x 80 mg/kg bw) based on 2/5 deaths until 48 hours after dosing and on lethality of all 5 females until 72 hours after dosing.

In the synopsis of the available data from single dose studies in rats and from repeated dose studies in rabbits, the rabbit appears more sensitive than the rat to the acute toxic effects of butanone oxime. Moreover, as specified in the guidance on haemolytic anaemia mortalities during days 0-3 in a repeated dose study may be considered for acute toxicity. Based on these data it is concluded that butanone oxime is acutely toxic by oral application (CLP Guidance, 3.9.2.5.2., Hematotoxicity).

Thus, the estimated ATE value is considered appropriate to conclude on the classification of MEKO.

RAC's response

Noted - following a careful consideration of all the available data, RAC shares the same view as the Dossier Submitter about the relevance of the studies in rabbits.

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	Spain	Berceo Chemicals SL	Please select organisation type..	21

Comment received

MEKO (butanone oxime) has a wide use in paints where it is used as the anti-skinning agent in alkyd paints since there is no real alternative. However, there have been no reported cases of acute toxicity in human use despite almost every household in Europe being exposed to it in the form of decorative paint. The report also makes it clear that the effects are species specific (page 23) "Taken together, comparing these LD50-values from the rat with rabbit data, the rabbit appears to be more sensitive than the rat to the toxic effects of butanone oxime." . Based on this statement human toxicity experience should be considered as the primary source of classification and when this is taken into account. Acute Tox. 3 for oral exposure and labelled with hazard statement H301: Toxic if swallowed.; with the pictogram "GHS06: Skull and crossbones", and with the signal word "Danger"; appears to be a gross over classification when considering the risk factors in its normal use. This shows a significant flaw in the current CLP regulations since we rely too much on test results which do not reflect the real risks or the real evidence from use of the products over a long period of time. There are many cases of this and yet nothing is being done to correct it. The ECHA has a duty to recommend that real life risk and experience is prioritized over dubious laboratory studies to bring some credibility back to the ECHA as an organisation.

Dossier Submitter's Response

The DS appreciates the comment by Berceo Chemicals. Please see comment no. 20.

RAC's response

RAC notes that the toxicity of butanone oxime cannot be assessed in humans. The absence of poisoning cases in the literature and during industrial experience does not inform sufficiently about the level of hazard this substance presents.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	22
Comment received				
<p>Hazard class Acute Tox. 3; H301 – Toxic if swallowed: FI CA agrees that butanone oxime has acute toxic properties. Criteria for classification as Acute Tox. 4 (H302) is met. FI CA considers that results from developmental toxicity study with repeated doses should not be used for Acute Tox. classification, because doses were not administered within 24 hours and pregnant animals are most likely more sensitive to toxicity. Therefore, FI CA does not support the proposed classification of Acute Tox. 3; H301 for butanone oxime.</p> <p>Hazard class Acute Tox. 4; H312 – Harmful in contact with skin: Acute dermal toxicity study conducted with butanone oxime resulted in LD50 value of 1848 mg/kg. The result meets the criteria for classification as Acute Tox. 4; H312. FI CA supports the proposed classification of Acute Tox. 4; H312 for butanone oxime.</p>				
Dossier Submitter's Response				
<p>The DS appreciates the comment by the FI MSCA regarding acute dermal toxicity.</p> <p>Regarding acute oral toxicity, please see comment no. 20.</p>				
RAC's response				
<p>Noted. Following a careful consideration of all the available data, RAC shares the same view as the Dossier Submitter about the relevance of the studies in rabbits.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	United Kingdom	Sensopolis Ltd	Company-Importer	23
Comment received				
<p>butanone oxime (MEKO) has a wide dispersive potential due to the wide range of paints it is used in as a primary anti skinning agent as there is no real viable alternative. However, in several decades of use there have been no reported cases of acute toxicity effects in humans. However, there is evidence that the effects are species specific (page 23) "Taken together, comparing these LD50-values from the rat with rabbit data, the rabbit appears to be more sensitive than the rat to the toxic effects of butanone oxime." and therefore at the very least human health experience should be taken into account. Acute Tox. 3 for oral exposure and labelled with hazard statement H301: Toxic if swallowed.; with the pictogram "GHS06: Skull and crossbones", and with the signal word "Danger"; seems to be an over classification when human experience considered and the risk factors in its normal use.(P25)</p>				
Dossier Submitter's Response				
<p>The DS appreciates the comment by Sensopolis Ltd.</p> <p>Please see comment no. 20. Reliable epidemiology studies or case reports of sufficient sizes, duration and quality (including robust exposure information), respectively, were not available to the DS.</p>				
RAC's response				
<p>Noted. The acute toxicity of butanone oxime cannot be assessed in humans. The absence of poisoning cases in the literature and during industrial experience does not inform</p>				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

sufficiently about the level of hazard this substance presents. Following a careful consideration of all the available data, RAC shares the same view as the Dossier Submitter about the relevance of the studies in rabbits.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	Spain	Iberica de Componentes Quimicos SL	Company-Importer	24

Comment received

MEKO has been used for more than 40 years in a wide range of alkyd derived coatings as an anti oxidant and anti skin, a role for which there is no real substitute. There has been no reported cases of any of the effects in the report during this time despite it being in regular use by the general public. The report states that the effects are species specific (page 23) "Taken together, comparing these LD50-values from the rat with rabbit data, the rabbit appears to be more sensitive than the rat to the toxic effects of butanone oxime." This is clear from the real life evidence, in humans we have not seen any of these clinical observations even at the coatings plants where you would expect the higher concentrations and repeat use to make them obvious, and yet there are none. Human experience should be taken into account and the proposal clearly over classifies MEKO. Acute Tox. 3 for oral exposure and labelled with hazard statement H301: Toxic if swallowed.; with the pictogram "GHS06: Skull and crossbones", and with the signal word "Danger"; Without any real evidence to the contrary, as with carcinogenic potential this is a rather dubious extrapolation especially when taking into account the most common form of exposure (inhalation) where it is classified on page 25 as follows: "Butanone oxime has not to be classified as acutely toxic by inhalation according to CLP." This at least is correct based on real life experience.

Dossier Submitter's Response

The DS appreciates the comment by Iberica de Componentes Quimicos.

Please see comment no. 20.

Reliable epidemiology studies or case reports of sufficient sizes, duration and quality (including robust exposure information), respectively, were not available to the DS.

RAC's response

Noted. The acute toxicity of butanone oxime cannot be assessed in humans. The absence of poisoning cases in the literature and during industrial experience does not inform sufficiently about the level of hazard this substance presents. Following a careful consideration of all the available data, RAC shares the same view as the Dossier Submitter about the relevance of the studies in rabbits.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	25

Comment received

We agree that no classification is warranted.

Dossier Submitter's Response

The DS appreciates the supporting comment by the FR MSCA

RAC's response

Noted. However, the observation of persistent irritant effects in an additional study submitted to ECHA by the REACH registrants' of butanone oxime meets the criteria for

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

category 2 classification for skin irritation. These results are available on ECHA's public dissemination database.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	26
Comment received				
We agree with the proposed classification as Eye Dam. 1 based on the irreversible effects. Nevertheless, could you please specify if the criterion of cornea opacity ≥ 3 is reached?				
Dossier Submitter's Response				
The DS appreciates the supporting comment by the FR MSCA.				
Unfortunately, no further details were reported specifying whether cornea opacity scores were ≥ 3 . The only details reported by the registrants were mentioned in the dossier (Irreversible effects on the eye: corneal opacity, iritis, conjunctival hyperaemia (scores: ≥ 2) in 6/6 animals at 24, 48, and 72 h after exposure; necrosis of the conjunctivae in 2/6 animals, not reversible at the end of observation period).				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	27
Comment received				
Eye irritation/corrosion study conducted with butanone oxime resulted in serious, irreversible eye effects. The results meet the criteria for classification as Eye Dam. 1; H318. FI CA supports the proposed classification of Eye Dam. 1; H318 for butanone oxime.				
Dossier Submitter's Response				
The DS appreciates the supporting comment by the FI MSCA.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Austria		MemberState	28
Comment received				
Despite conflicting results of different test guidelines (GMPT and LLNA) we think that Skin Sens. 1B H317 is justified. Maybe these conflicting results are due to basic differences between these tests. LLNA measures lymphocyte proliferation after topical application of the test substance Induction phase. The GPMT is an adjuvant-type test in which the acquisition of sensitisation is potentiated by the use of Freund's Complete Adjuvant (FCA) and in which both intradermal and topical exposure are used during the induction phase. In addition also Acetone oxime, a structural similar compound is negative in the LLNA but positive in the GPMT.				
Dossier Submitter's Response				
The DS appreciates the supporting comment by the Austrian MSCA.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	29

Comment received

The concentrations used for intradermal induction (> 1%) and the incidence of sensitized guinea pig (> 50%) reported in the GPMT and Buehler assays are very high. In this context, although the criteria for classification to subcategory 1B are fulfilled, the classification for subcategory 1A cannot be excluded and therefore no subcategory could be proposed. Thus, we consider that the substance should be classified as a Category 1 skin sensitizer (without subcategory).

Dossier Submitter's Response

The DS appreciates the comment by the FR MSCA. However, the DS does not concur with the conclusion.

In comparison to the given criteria for the hazard category and sub-categories for skin sensitisation according to CLP butanone oxime fulfils the criteria for classification in the hazard class as skin sensitizer Sub-category 1B, H317 according to table 3.4.4 of the CLP Regulation, because a skin sensitisation response of $\geq 30\%$ at $> 1.0\%$ intradermal induction dose was observed in the adjuvant type test method (GPMT) in the key and a supporting study. Moreover, in the non-adjuvant type test method (Buehler assay) a skin sensitisation response of $\geq 15\%$ at $> 20\%$ topical induction was observed, which is in accordance with the CLP criteria for classification as Skin Sens 1B as well.

Criteria for classification as Skin Sens 1A, on the other hand, were considered not fulfilled, as the induction doses applied in the tests are higher than the threshold doses for classification as Cat. 1A reported in the CLP Regulation (GPMT: induction dose $> 1\%$; Buehler assay: induction dose $> 20\%$). Whether lower induction doses might have elicited a sufficient sensitising response after exposure to the challenge dose is considered speculation.

RAC's response
The comment from FR is in line with CLP guidance and the established practice of RAC.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2017	Netherlands		MemberState	30

Comment received

- Although the results of the Buehler and GPMT studies comply with the classification criteria of sub-category 1B, there are no data with induction doses that comply with the criteria of sub-category 1A. Especially considering the high response rates in some of the studies, it cannot be excluded that response rates at lower induction doses would be high enough to fulfill the criteria of 1A. The negative LLNA test contradicts with the results of the other tests and we agree that therefore less weight should be given to this result. An assessment of the potency based on the result of the MEST test would require a justification as no criteria are available for sub-classification in the legislation or the guidance. Therefore, due to a lack of data regarding low induction concentrations in the Buehler and GPMT, we do not agree with the subcategorization in 1B for skin sensitization and propose that the classification remains Skin cat 1

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

Dossier Submitter's Response				
The DS appreciates the comment by the NL MSCA. However, the DS does not concur with the conclusion and is looking forward to the discussion at RAC. Please see comment no. 29.				
RAC's response				
The comment from NL is in line with CLP guidance and the established practice of RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	31
Comment received				
Butanone oxime currently has harmonised classification of Skin Sens. 1; H317. The dossier submitter proposes classification into sub-category 1B. FI CA considers that the data is not sufficient for classification into sub-categories. The results of two Guinea Pig Maximization tests and one Buehler assay fulfill the criteria for classification into sub-category 1B. However, the tested concentrations were not low enough to exclude classification into sub-category 1A. Also, the sensitisation rates with tested concentrations were high, which indicates that sub-category 1A cannot be excluded. FI CA supports the current classification of Skin Sens. 1; H318 for butanone oxime.				
Dossier Submitter's Response				
The DS appreciates the comment by the FI MSCA. However, the DS does not concur with the conclusion. Please see comment no. 29.				
RAC's response				
The comment from FI is in line with CLP guidance and the established practice of RAC.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Austria		MemberState	32
Comment received				
According to literature transient narcosis is a common effect in laboratory animals for low molecular weight oxime compounds (Derelanko and Rusch, 2008). Based on the experimental evidence presented in the CLH report we support classification with STOT SE 3, H336.				
We further suggest a discussion concerning STOT RE because of the borderline effects on the hematopoietic system in comparison with the CLH criteria.				
Derelanko M & Rusch G (2008). Oxime silanes: structure/toxicity relationships, Drug and Chemical Toxicology, 31:97-114, 2008				
Dossier Submitter's Response				
The DS appreciates the supporting comments by the Austrian MSCA.				
The DS further supports a discussion on the classification of MEKO as STOT RE based on the mentioned haematotoxicity results, as effects might be considered as borderline. Please see also comment no. 4.				
RAC's response				
RAC agrees that the criteria for STOT SE 3; H336 are met by consistent findings in several animal studies.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUTANONE OXIME; ETHYL METHYL KETOXIME; ETHYL METHYL KETONE OXIME

After a careful review of all the available data, RAC is of the opinion that the criteria for STOT RE 2 for the blood system are met (see Opinion Document).

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2017	France		MemberState	33
Comment received				
We consider that the Derelanko et al (2003) study is not relevant for classification as STOT SE since the behavioural effects are reported at doses which already produce a high level of lethality. Anyway, we agree with the proposed classification based on the other available toxicity studies in animals.				
Dossier Submitter's Response				
The DS appreciates the supporting comments by the FR MSCA.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS

1. COMMENTS TO PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING.pdf [Please refer to comment No. 8, 18]
2. Dr Dekant - Expert review-MEKO.pdf [Please refer to comment No. 1, 9]

CONFIDENTIAL ATTACHMENTS

1. WD-MEKO.pdf [Please refer to comment No. 3, 11]