Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

4-methylpentan-2-one; isobutyl methyl ketone

EC Number: 203-550-1
CAS Number: 108-10-1

CLH-O-0000001412-86-295/F

Adopted

20 September 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4-METHYLPENTAN-2-ONE; ISOBUTYL METHYL KETONE

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: 4-methylpentan-2-one; isobutyl methyl ketone
EC number: 203-550-1
CAS number: 108-10-1
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	1
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
See responses to comments No. 4 and 21.				
RAC's response				
See responses to comments No. 3 and 21.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
24.01.2019	Germany		MemberState	2
Comment received				
The malignant mesenchymal tumours in the kidneys of female rats can be regarded as the decisive effect in determining the classification as Carcinogenic, Category 2 H351. However, since the incidences were low and only slightly above the historical control data, this is a borderline case. The DE CA considers classification as Carc. 2; H351 as appropriate. However, based on the limited evidence non-classification may also be discussed as an option.				
Dossier Submitter's Response				
Thank you for this comment.				

RAC's response
Thank you for this comment.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	United Kingdom	<confidential>	Industry or trade association	3

Comment received

See attached report

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MIBK OSPA CLP.zip

Dossier Submitter's Response

1) liver tumors – CAR mediated

As discussed in the CLH dossier the hepatocellular adenomas/carcinomas seen in mice after administration of 4-methylpentan-2-one were not considered relevant for humans. Based on the available data a CAR/PXR mediated MoA can be assumed. The lack of mechanistic testing in human cells was mentioned for completeness.

2) kidney toxicity observed in female rats

Unfortunately an error occurred in the conclusions (Chapter 10.9.3), however, the concern is described correctly in the text in Chaper 10.9.1("*However exposure-related increased incidences of chronic nephropathy in female rats indicate that exposure-related nephropathy also may occur independent of the α2u-globulin mechanism. But no tumours were seen in females*."), in Table 19 and in Chapter 10.9.2 ("*In addition the finding of chronic nephropathy in exposed female rats shows that an additional mechanism inducing renal toxicity is present and could also be involved in the formation of tumours seen in males.")*

The wording in the conclusions (Chapter 10.9.3) should be the following: "*There are some indications that kidney tumours seen in male rats are caused by a α2u-mediated MoA, however, as there is also some kidney toxicity seen in female* ***F344/N rats*** *another mechanism may also be involved in the tumour formation. A recent review identified some uncertainties regarding the link between α2μ and kidney tumour formation*."

3) Uncertainties regarding the link between α2u-globulin and kidney tumors

The criteria from US EPA and IARC have been evaluated in the dossier with the conclusion that *"mechanistic studies are available and criteria defined by IARC, 1999 are met".* However, uncertainty was indicated by increased incidences of chronic nephropathy in female rats as well as by IARC (2013): "*…the strength of the evidence that male rat kidney tumours arose through a α2u-globulin nephropathy mechanism is weak…..the relevance of the tumour response to humans cannot be excluded."*
All relevant information, including uncertainties, was compiled and presented in the report.

4) Tumors seen at other sites

As documented in the publication by Maronport (2016) the problem around MNCL in F344 rats is well known and resulted in a change from F344 rats to Sprague Dawley rats for

NTP studies in 2006. However, the available study for 4-methylpentan-2-one was finalized in February 2007 aware of this issue.
Maronpot (2016) stated that the correct historical control data is essential for interpretation of results. In the NTP-study it is clearly indicated that the conditions in the historical control database have been similar (diet NTP-2000, same route of exposure).
The study authors summarized that "*Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure*."
The incidence of MNCL showed a dose response with a statistical significance of p≤0.05 at the highest dose and "*Incidences of this common neoplasm in the chamber control group of animals were not different from those observed in the chamber controls in the historical database."*

RAC's response

Thank you for the comment and DS's response.
Concerning liver tumours, RAC agrees with the DS that CAR/PXR mediated MoA can be assumed. Nevertheless, whether the absence of human in vitro leads to major uncertainties for non human relevance will be discussed at RAC meeting.

Concerning kidney toxicity, the typo is noted.

About α2u-globulin and kidney tumours. RAC agrees that the presence of chronic nephropathy in female mice leads to uncertainties on the proposed MoA. This MoA in line with non human relevance will be discussed at RAC meeting.

RAC agrees that with regards to tumours at other sites, historical control provided in the NTP study should be considered. As the tumours were only slightly above the historical control, the weight of these tumours type in the overall WOE for classification is weak.

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	4

Comment received

The agency is proposing the addition of a Carcinogen Category 2 (H351) classification for MIBK, with which the Panel respectfully disagrees. (CLH Report- Page 28)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip

Dossier Submitter's Response

1) <u>liver tumors – CAR mediated</u>

As discussed in the CLH dossier the hepatocellular adenomas/carcinomas seen in mice after administration of 4-methylpentan-2-one were not considered relevant for humans. Based on the available data a CAR/PXR mediated MoA can be assumed. The lack of mechanistic testing in human cells was mentioned for completeness.

2) <u>kidney toxicity observed in female rats</u>

Unfortunately an error occurred in the conclusions (Chapter 10.9.3), however, the concern is described correctly in the text in Chaper 10.9.1("*However exposure-related increased incidences of chronic nephropathy in female rats indicate that exposure-related*

nephropathy also may occur independent of the α2u-globulin mechanism. But no tumours were seen in females."), in Table 19 and in Chapter 10.9.2 ("*In addition the finding of chronic nephropathy in exposed female rats shows that an additional mechanism inducing renal toxicity is present and could also be involved in the formation of tumours seen in males.")*

The wording in the conclusions (Chapter 10.9.3) should be the following: "*There are some indications that kidney tumours seen in male rats are caused by a α2u-mediated MoA, however, as there is also some kidney toxicity seen in female* ***F344/N rats*** *another mechanism may also be involved in the tumour formation. A recent review identified some uncertainties regarding the link between α2μ and kidney tumour formation*."

3) Uncertainties regarding the link between α2u-globulin and kidney tumors

The criteria from US EPA and IARC have been evaluated in the dossier with the conclusion that *"mechanistic studies are available and criteria defined by IARC, 1999 are met".* However, uncertainty was indicated by increased incidences of chronic nephropathy in female rats as well as by IARC (2013): "*…the strength of the evidence that male rat kidney tumours arose through a α2u-globulin nephropathy mechanism is weak…..the relevance of the tumour response to humans cannot be excluded."*
All relevant information, including uncertainties, was compiled and presented in the report.

4) Tumors seen at other sites

As documented in the publication by Maronport (2016) the problem around MNCL in F344 rats is well known and resulted in a change from F344 rats to Sprague Dawley rats for NTP studies in 2006. However, the available study for 4-methylpentan-2-one was finalized in February 2007 aware of this issue.
Maronpot (2016) stated that the correct historical control data is essential for interpretation of results. In the NTP-study it is clearly indicated that the conditions in the historical control database have been similar (diet NTP-2000, same route of exposure).
The study authors summarized that "*Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure*."
The incidence of MNCL showed a dose response with a statistical significance of $p \leq 0.05$ at the highest dose and "*Incidences of this common neoplasm in the chamber control group of animals were not different from those observed in the chamber controls in the historical database."*

RAC's response

See RAC's response to comment 3.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	Slovenia		Individual	5

Comment received

In my opinion, the quality of the test material is crucial for any reliable conclusions. Unfortunately in the case of this substance both of the animal studies on which proposed classification for carcinogenicity is based bears no information on the purity of the test material. Even worse it is well known that the manufacturing process of this material includes the transformation of mesityl oxide (4-methylpent-3-en-2-one) intermediate which is hydrogenated to 4-methylpentan-2-one (e.g. usual manuf. process is presented even in Wikipedia).

As well it is known for mesityl oxide that it is toxic and as it is alpha,beta-unsaturated ketone it could not be excluded as carcinogen although it is not classified so. It possible that some traces of untransformed mesityl oxide causes some distortions in the result of test. I think all the tests made with 4-methylpentan-2-one should exclude the presence of substantial amount of mesityl oxide. As a conclusion I think the both tests on which proposed classification of 4-methylpentan-2-one lay on are not sufficient reliable to classify the substance as Carc. Cat. 2.
Dossier Submitter's Response
Unfortunately the purity of the test substance is not stated in the CLH-Dossier. For the cited NPT-study (2007) the identity and the purity of the test substance was analysed. The chemical, a colorless liquid, was identified as 4-methylpentan-2-one by infrared and proton nuclear magnetic resonance spectroscopy. The purity of the lot was determined by elemental analysis and gas chromatography. The overall purity was determined to be greater than 99%.
RAC's response
Thank you for your comment. Purity in the NTP study was 99 %. The presence of mesityl oxide as an impurity, not classify for carcinogenicity, may not impact the results of the study.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	Finland		MemberState	6
Comment received				
Proposed classification for the isobutyl methyl ketone is Carc 2, H351 - Suspected of causing cancer, based on the increased incidence of kidney carcinomas in rats by a α2μ-globulin related mechanism and the liver carcinomas in mice by a CAR/PXR -mediated mechanism. Also renal mesenchymal tumours were seen in female rats (4 % vs. 0,0 % in current control and 0,0 % in historical control data), a dose-related increase of mononuclear cell leukemia in male rats (70 % vs. 50 % in current control and 47,1 % in historical control data) and dose-related increase of pheochromocytoma in male rats (28 % vs. 16 % in current control and 17 % in historical control data). The tumours were restricted to one sex and one species and were only slightly above or in the upper range of historical control data. Both a α2μ-globulin related and a CAR/PXR-mediated mechanisms are not considered to be a predictor of carcinogenic risk to humans as α2μ-globulin protein is missing in humans and there are clear species differences in CAR activation which severely hamper's the extrapolation of animal data to humans. However,there is also some kidney toxicity seen in female mice and another mechanism may also be involved in the tumour formation and there are some uncertainties regarding the link between α2μ-globulin and kidney tumour formation. In a weight of evidence approach it cannot be exluded that isobutyl methyl ketone has a carcinogenic potential for humans. The FI CA considers that classification as Carc 2, H351 can be justified.				
Dossier Submitter's Response				
Thank you for this support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	France	MIBK REACH consortium, represented by Arkema France	Industry or trade association	7

Comment received

MIBK REACH consortium disagrees with the CLH proposal for classifying MIBK for Carcinogenicity Category 2.
SEE ATTACHED DOCUMENTS (PUBLIC & CONFIDENDIAL) FOR DETAILS ON THE ARGUMENTATION.
The Environment Agency Austria recognized that the MIBK-induced liver tumors were CAR-mediated and the male rat kidney tumors were α2u-globulin mediated. However, they concluded that the evidence is not sufficient to exclude human relevance. This is contradictory to ECHA's position. ECHA has accepted the alpha-2u-globulin MOA as well as the CAR/PXR MOA for other chemicals that act through one, or both of these MOAs and concluded that kidney effects associated with alpha-2u-globulin nephropathy and male rat renal tumors are not relevant for human health risk assessment and classification in its evaluation for other chemicals like carvone, dodecane and tetrahydrofuran (ECHA, 2013, ECHA 2018a, ECHA 2018b). Also, according to both the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (US EPA), chemically induced renal neoplasms in male rats, developed coincident with α2u-globulin nephropathy, are not considered predictive of risk to humans (IARC 1999 Consensus report; Swenberg and Lehman-McKeeman1999; US EPA 1991). The observed MIBK-induced liver effects are analogous to phenobarbital (PB)-induced effects, with CAR/PXR activation as the common initiating event leading to mouse liver tumors (Hughes et al 2016). In addition, several papers using known CAR/PXR activators such as PB (Elcombe 2014; Yamada et al 2014, Friedman GD, et al. 2009; IARC 2001; La Vecchia al. 2014; Lake BG. 2009) have demonstrated CAR/PXR activation is not mitogenic to the human liver, using human hepatocytes in chimeric mice and epidemiological studies of human populations chronically exposed to PB.

Altogether, there is a strong weight-of-evidence (WOE) in peer-reviewed literature that is supportive of a CAR-mediated activation in rodents that has limited, if any, relevance to humans. Accordingly, we propose Environment Agency Austria reconsider the addition of Carcinogen Category 2 (H351) classification to MIBK due to the lack of human relevance
Note: The Environment Agency Austria refers to the protein α2u-globulin as α2μ-globulin which is a different protein that is not in the scope of the current document. For consistency and accuracy, the consortium will refer to it as α2u-globulin.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment PUBLIC consortium comments on CLH Proposal for MIBK_final.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL consortium comments on CLH Proposal for MIBK_final 20190125.pdf

Dossier Submitter's Response

1) <u>liver tumors – CAR mediated</u>

The comments (attachment) give an overview on discussions around CAR/PXR mechanisms and human relevance. As discussed in the CLH dossier the hepatocellular adenomas/carcinomas seen in mice after administration of 4-methylpentan-2-one were

not considered relevant for humans. Based on the available data a CAR/PXR mediated MoA can be assumed. The lack of mechanistic testing in human cells was mentioned for completeness.

2) kidney toxicity observed in female rats

Unfortunately an error occurred in the conclusions (Chapter 10.9.3), however, the concern is described correctly in the text in Chaper 10.9.1("*However exposure-related increased incidences of chronic nephropathy in female rats indicate that exposure-related nephropathy also may occur independent of the α2u-globulin mechanism. But no tumours were seen in females*."), in Table 19 and in Chapter 10.9.2 ("*In addition the finding of chronic nephropathy in exposed female rats shows that an additional mechanism inducing renal toxicity is present and could also be involved in the formation of tumours seen in males.")*

The wording in the conclusions (Chapter 10.9.3) should be the following: "*There are some indications that kidney tumours seen in male rats are caused by a α2u-mediated MoA, however, as there is also some kidney toxicity seen in female* ***F344/N rats*** *another mechanism may also be involved in the tumour formation. A recent review identified some uncertainties regarding the link between α2μ and kidney tumour formation*."

The wording α2u as well as α2μ (especially in older literature) is used in literature in connection with nephropathy in male rats. A wording as α2u can be followed.

3) Uncertainties regarding the link between α2u-globulin and kidney tumors

The criteria from US EPA and IARC have been evaluated in the dossier with the conclusion that *"mechanistic studies are available and criteria defined by IARC, 1999 are met".* However, uncertainty was indicated by increased incidences of chronic nephropathy in female rats as well as by IARC (2013): "*…the strength of the evidence that male rat kidney tumours arose through a α2u-globulin nephropathy mechanism is weak…..the relevance of the tumour response to humans cannot be excluded."*
All relevant information, including uncertainties, was compiled and presented in the report.

4) Tumors seen at other sites

As documented in the publication by Maronport (2016) the problem around MNCL in F344 rats is well known and resulted in a change from F344 rats to Sprague Dawley rats for NTP studies in 2006. However, the available study for 4-methylpentan-2-one was finalized in February 2007 aware of this issue.
Maronpot (2016) stated that the correct historical control data is essential for interpretation of results. In the NTP-study it is clearly indicated that the conditions in the historical control database have been similar (diet NTP-2000, same route of exposure).
The study authors summarized that "*Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure*."
The incidence of MNCL showed a dose response with a statistical significance of $p \leq 0.05$ at the highest dose and "*Incidences of this common neoplasm in the chamber control group of animals were not different from those observed in the chamber controls in the historical database."*

RAC's response

See RAC's response to comment No 3.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	Sweden		MemberState	8

Comment received

We agree that no classification of 4-methylpentan-2-one in germ cell mutagenicity is warranted. However, we do not agree that results were clearly negative in the two Ames tests and the in vivo micronucleus test. We prefer that it is stated in the CLH-report and/or RAC-opinion that classification is not warranted due to insufficient data.

Regarding the two Ames test:
- Substances should be tested up to cytotoxic concentrations up to 5 mg/plate or 5 ml/plate according to OECD TG 471. In the study by O'Donoghue (1988) no cytotoxicity in the main study at doses up to 4 ul/plate were observed. In the study by Brooks (1988) no cytotoxicity at tested concentrations up to 4 mg/plate was reported.
- There was no valid positive control in the study by Brooks (1988).
- TA102 or E.coli strain WP2 uvrA were not included in the study by O'Donoghue (1988).
- Thus, the results from the two Ames tests cannot be considered as conclusively negative.

Regarding the in vitro gene mutation study in mouse lymphoma cells (OECD TG 476):
- There were obvious problems with variation in the 2nd test (-S9) between the duplicates. Cell growth and mutant frequencies varied up to approx. 40% between the duplicates.
- According to OECD TG 476 the highest concentration should aim to achieve between 20 and 10% RS. Care should be taken when interpreting positive results only found at 10% RS or below: Thus, in both tests without metabolic activation in the study by O'Donoghue (1988) the highest concentrations chosen were too toxic (total growth <10%) and the second highest doses did not cause cytotoxicity at the level recommended in the test guideline (cell growth was >30%).
- At two concentrations in both the first and the second test in the O'Donoghue study, there were statistically significant increases (approx. two times), in mutant frequencies compared with concurrent negative control. However, no there was no concentration-related increase. Nevertheless, according to the test guideline a test chemical is considered to be positive if at least one of the test concentrations exhibits a statistically significant increase compared with the concurrent negative control.
- Thus, the results give an indication of a mutagenic potential of the test substance.
- An appropriate follow up to a positive result in this study would be an in vivo test of gene mutations in vivo (e.g. Comet assay or TGR), not a test for cytogenic aberration (as available in the current CLH-proposal).

Regarding the in vitro chromosomal aberration study in rat liver cells (OECD TG 473):
- No cytotoxicity at any dose was reported.
- No metabolic activation was used.
- Thus, the results from this study is not sufficient to conclude on the mutagenic potential of the test substance.

Regarding the in vivo micronucleus test (similar to OECD TG 474):
- i.p. administration was used which is not a recommended route of administration according to OECD TG 474 or CLP guidance.
- Only one dose was tested, and the administered dose caused excessive toxicity since heavy sedation (2/5 males) and mortality (4/5 females) was observed.

- It was unclear if target organ was reached by the substance.
- Thus, the results from this study is not sufficient to conclude on the mutagenic potential of the test substance.

Dossier Submitter's Response

It is correct that the studies have some deficiencies; they have been described in the CLH-report but are not well reflected in the summary. We also agree that the substance is not clearly negative tested in most of the studies due to inappropriate study design (missing cytotoxicity, administration, positive control, etc.). It should not be stated as "clear negative" in the CLH report but the overall picture of the substance including the metabolites shows a lack of mutagenicity.

OECD TG 476: According to the test guideline a chemical is considered to be positive if at least one of the test concentrations exhibits a statistically significant increase compared to control and the increase is concentration related. Also considering the variations between the duplicates the available test cannot be evaluated as positive.

OECD 474: For this study the test substance was administered i.p. (not recommended as it is not the intended route of human exposure). A study by DiVincenzo (1976, see CLH report) showed that after i.p. administration of 4-methylpentan-2-one to guinea pigs the two metabolites can be detected in the serum. The half-life of 4-methylpentan-2-one was 66 min and the clearance time was 6h. The main metabolite 4-hydroxy-4 methyl-2-pentanone was cleared in 16 h. The concentration of 4-methyl-2-pentanol was too low for quantitation. The amount of substance and metabolite in the blood compartment at 1h after dosing has been estimated by summing their respective concentrations in serum. For 4-methylpentan-2-one abaut 1.8% of the original dose were found in the blood compartment.

To include the shortcomings in the summary Chapter 10.8.2 should be read as following:

4-methylpentan-2-one was negative in two bacterial reverse mutation assays (O`Donoghue, 1988; Brooks, 1988), however, no cytotoxicity at tested concentrations was seen and positive control was not valid in one study. A chromosome aberration study in rat liver cells was negative but missing cytotoxicity and metabolic activation weaken the result (Brooks, 1988). An in vitro Mammalian Cell Gene Mutation Test in mouse lymphoma cells was negative with metabolic activation but gave equivocal results without metabolic activation (positive response without dose-response relationship) (O`Donoghue, 1988). The substance did not induce unscheduled DNA synthesis in mammalian cells in vitro (O`Donoghue, 1988) and a Gene Mutation Assay in Saccharomyces cerevisiae was negative (Brooks, 1988). In the in vivo micronucleus test in mice intraperitoneal injection of 4-methylpentan-2-one was negative when tested at one very toxic concentration (O'Donoghue, 1988).
Negative results are supported by data of the metabolites 4-hydroxy-4 methyl-2-pentanone (CAS 123-42-2) and 4-methyl-2-pentanol (CAS 108-11-2) also showing a lack of mutagenic activity.

RAC's response

RAC agrees that there is limitations in the database and that equivocal gene mutation results obtained *in vitro* with the substance without S9 may not have been appropriately followed-up *in vivo*. Nevertheless, Based on the available database, no classification is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	9
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	10
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2019	France		MemberState	11
Comment received				
Acute toxicity section 10.3.2 page 13 : it seems that there is a mistake in the report of the interpretation criteria for Acute Tox : It is written in the dossier: "According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as - Acute Tox 4 (inhal) if the LC50 values are > 2.0mg/l and ≤ 10mg/l (4h exposure) - Acute Tox 3 (inhal) if the LC50 values are > 10.0mg/l and ≤ 20.0 mg/l (4h exposure)" Instead, Acute Tox 3 should be recommended if the LC50 values are > 2.0mg/l and ≤ 10mg/l (4h exposure) and acute Tox 4 if the LC50 values are > 10.0mg/l and ≤ 20.0 mg/l (4h exposure) Therefore based on the data analysed and the toxicity range reported, as in the Smyth (1951) study, no mortality was observed at 8.2 mg/l and 100% at 16.4 mg/l, it cannot be				

excluded that the LC50 is below 10 mg/L and therefore a category Acute Tox3 could also be justified.
Dossier Submitter's Response
It is correct that there is a mistake in the criteria for classification (sction 10.3.2). They should be as following: • Acute Tox **3** (inhal) if the LC_{50} values are > 2.0mg/l and ≤ 10mg/l (4h exposure) • Acute Tox **4** (inhal) if the LC_{50} values are > 10.0mg/l and ≤ 20.0 mg/l (4h exposure) Unfortunately there is only limited information on study results available and a detailed evaluation was not possible. The LD_{50}-value determined by Smyth (1951) was in the range of 8.2 mg/l < LC50 > 16.4 mg/l. While no mortality was observed at the lower concentration all animals died (6/6) at 16.4 mg/l within 14 days. It is correct that an LC_{50} below 10 mg/l cannot be excluded however taking into consideration all the other acute toxicity data a classification as Acute Tox 4 seems to be more appropriate.
RAC's response
The typo is noted. RAC agrees that, strictly classification as category 3 would be warranted. Nevertheless, RAC agrees with the DS of rht efollowing reasons: - other acute toxicity data supported a classification as Acute tox. 4, - no mortality was observed at 8.2 mg/L.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	Finland		MemberState	12
Comment received				
Isobutyl methyl ketone has a harmonized classification as Acute Tox 4*, H332 for the inhalatory route. The FI CA supports that there is sufficient evidence to remove the asterisk from the classification as the ATE is determined to be 11 mg/l. According to the Table 3.1.1. of CLP regulation a substance shall be classified as Acut tox 4, H332 if the ATE value is > 10 mg/l and ≤ 20,0mg/l.				
Dossier Submitter's Response				
Thank you for this support.				
RAC's response				
Thank you for this comment.				

Date	Country	Organisation	Type of Organisation	Comment number
24.01.2019	Germany		MemberState	13
Comment received				
The proposed removal of the asterisk and re-classification as Acute Tox. 4; H332 is supported.				
Dossier Submitter's Response				
Thank you for this support.				
RAC's response				
Thank you for this comment.				

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	14
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	15
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	16
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	17
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant. Response to attachment see comment No 3.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2019	France		MemberState	18
Comment received				
STOT SE H336: The dossier submitter considered that reduction in duration of immobility reported in the study of DE Ceaurriz, 1984 may be due to narcosis (table 33) whereas it should be the other way round: decrease in mobility duration. Therefore, the justification of a category STOT SE 3 H336 cannot be supported by this observation.				
Dossier Submitter's Response				
The study by De Ceaurriz (1984) - where a decrease in immobility time (ID_{50}) was used as an indicator of the behavioural toxicity - was presented for completeness. The results of such a forced swim test are discussed controversial and may be related to (anti-) depression, stress-related immobility or an adaptive learning process of the rodents. Therefore the study was not used to support the classification for STOT SE 3, H336 (see chapter 10.11.2).				
RAC's response				
The justification of the classification is not only based on this study. This is mainly based on human data and also supported by clear effects observed in rats, mice and guinea pigs.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	Finland		MemberState	19
Comment received				
Isobutyl methyl ketone is already classified for causing respiratory track irritation (STOT SE 3, H335) and that is indicated in both animal and human studies. Also acute narcotic effects after acute and repeated exposure have been indicated in animal studies and industry health records. Hence the FI CA supports the proposed addition as STOT SE 3, H336 - May cause drowsiness or dizziness.				
Dossier Submitter's Response				
Thank you for this support.				

RAC's response
Thank you for this comment.

Date	Country	Organisation	Type of Organisation	Comment number
24.01.2019	Germany		MemberState	20
Comment received				
The proposed classification as STOT SE 3; H336 is supported.				
Dossier Submitter's Response				
Thank you for this support.				
RAC's response				
Thank you for this comment.				

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	21
Comment received				
The Panel is in support of the Environment Agency Austria's CLH proposal for adding a STOT-RE category 3 (H336) classification for narcotic effects to MIBK. (CLH Report- Page 58) ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
We think the ACC panel is talking about a classification for STOT **SE** 3, H336. Thank you for this support.				
RAC's response				
Thank you for this comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	22
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. See also coment No 21. For response to attachment see comment No 4.				
RAC's response				
Not relevant.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2019	France	MIBK REACH consortium, represented by Arkema France	Industry or trade association	23
Comment received				
MIBK REACH consortium supports the Environment Agency Austria's CLH proposal for classifying MIBK as STOT-RE category 3 (H336) for narcotic effects. ECHA note – An attachment was submitted with the comment above. Refer to public attachment PUBLIC consortium comments on CLH Proposal for MIBK_final.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL consortium comments on CLH Proposal for MIBK_final 20190125.pdf				
Dossier Submitter's Response				
We think the MIBK REACH consortium is talking about a classification for STOT **SE** 3, H336. Thank you for this support.				
RAC's response				
Thank you for this comment.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2019	United States	American Chemistry Council- Ketones Panel	Industry or trade association	24
Comment received				
Not Relevant ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Ketones Panel-MIBK zip.zip				
Dossier Submitter's Response				
Not relevant. Response to attachment see comment No. 4.				
RAC's response				
Not relevant.				

PUBLIC ATTACHMENTS
1. MIBK OSPA CLP.zip [Please refer to comment No. 3]
2. PUBLIC consortium comments on CLH Proposal for MIBK_final.pdf [Please refer to comment No. 7, 23]
3. ACC Ketones Panel-MIBK zip.zip [Please refer to comment No. 1, 4, 9, 10, 14, 15, 16, 17, 21, 22, 24]

CONFIDENTIAL ATTACHMENTS
1. CONFIDENTIAL consortium comments on CLH Proposal for MIBK_final 20190125.pdf [Please refer to comment No. 7, 23]