Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Cumene

EC Number: 202-704-5
CAS Number: 98-82-8

CLH-O-0000006849-56-01/F

Adopted

17 September 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CUMENE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 26.11.2019

Substance name: cumene
EC number: 202-704-5
CAS number: 98-82-8
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Belgium	ReachCentrum on healf of the Phenols & Derivatives Reach Consortium	Industry or trade association	1
Comment received				
The Cumene Registrants note that the toxicokinetics section of the CLH proposal does not address the fact that certain metabolic pathways for cumene are saturated in the rat and mouse at high doses, resulting in the initiation of MoAs unique to those doses and not quantitatively relevant to human exposures. This omission is relevant to interpretation of the marginal increase in liver tumours in female mice exposed to 500 ppm cumene. Comments address Section 9 (p. 7-12) of the CLH Proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cumene_PandD-Cons_Carcinogenicity_November 2019.zip				
Dossier Submitter's Response				
Thank you for your comments, to which we respond as follows. Saturation of metabolism pathways: A higher percentage of exhaled radioactivity was observed in the inhalation study of Research Triangle Institute (1989) in male and female rats at 1200 ppm, with a slight increase already at 500 ppm in female rats. The exhaled radioactivity was analytically determined as cumene. This might indicate a saturation of metabolic pathways. No information is available about a shift towards critical metabolic pathways under these conditions. No such information is available for inhalation exposure in mice. In the study by (Chen *et al.*, 2011) an increased exhalation of radioactivity in male and female mice was seen at 1000 mg/kg administered by gavage. However, such bolus application cannot be considered to be equivalent to inhalation over prolonged time periods (6 hours). Following the commentator's route-to-route calculation the single oral dose of 1000 mg/kg would be equivalent to an inhalation concentration of 500 ppm for an exposure period of 6 hours. But the same dose would be equivalent to a concentration of 6000 ppm over 30 min. In conclusion, no convincing evidence is available showing that metabolic saturation in female mice is achieved at 500 ppm.				

Available data provide evidence that at these high doses (1000 mg/kg) exhalation of unchanged cumene is increased. The commentator argues that the high doses are "resulting in the initiation of MoAs unique to those doses". However, no evidence is available on the nature of the initiated MoAs and no information is available whether shifts in metabolic pathways occur which would lead to non-linear kinetics for the relevant metabolic pathways, i.e. a disproportionate increase in toxic metabolites.
With regard to the commentator's argument that the tested exposure concentrations are not quantitatively relevant to human exposures, we remark that according to the ECHA Guidance on the Application of the CLP criteria high exposure levels in the experimental studies above human-relevant exposures is not an argument on its own, as long it does not lead to excessive toxicity, as the classification follows a hazard- and not a risk-based approach.

Other comments:
We agree that Chen *et al.* (2011) can be added to Table 9 under "Absorption", further adding evidence to the notion on ready absorption. Your suggestions for Table 9 will be carefully considered. With regard to the higher concentration of radioactivity found by Chen *et al.* in the mouse lung indeed the findings from *in vitro* studies with microsomes can be taken as an indication that the radioactivity at least partly consists of metabolites M14, M15, and AMS (see also discussion on MoA for lung tumours, below).

RAC's response

Thank you. RAC fully agrees with the response provided by the dossier submitter.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	United States		Individual	2

Comment received

We note that the toxicokinetics section of the CLH proposal does not address the fact that the metabolism of cumene is saturated in the rat and mouse at high doses, resulting in potential initiation of MoAs unique to those doses and not quantitatively relevant to human exposures. Cumene metabolism is saturated in male rats between 500 and 1,200 ppm; in female rats, saturation is clearly present at both 500 ppm and 1,200 ppm exposures. Saturation of cumene metabolism also was readily apparent after oral dosing of male and female mice at 1000 mg/kg/day, which is approximately equal to a 500 ppm 6 hr inhalation exposure. The onset of metabolically-saturating doses results in a change in the slope of the dose-response curve and is termed a Kinetically-Derived Maximum Dose (KMD). Because real-world human exposures are substantially less than those associated with the KMD in rats and mice, observation of toxic effects (including cancer) at doses that exceed the KMD are not regarded as quantitatively relevant to human hazard and risk characterization as per guidance of OECD and ECHA (OECD, 2011; ECHA, 2017). Omission of the toxicokinetic saturation data is relevant to interpretation of the marginal increase in liver tumours observed only in female mice that had been exposed to the metabolically-saturated 500 ppm cumene.

Organisation for Economic Cooperation and Development (OECD). 2011. OECD guideline for the testing of chemicals. No. 443. Extended one-generation reproductive toxicity study. 28 July 2011.
European Chemicals Agency (ECHA). 2017. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7c: Endpoint specific guidance. Version 3.0. June

2017. Comments address Section 9 (p. 7-12) of the CLH Proposal.
Dossier Submitter's Response
Thank you for your response. As the issues targeted are essentially the same as those addressed in comment #1 we refer to the responses given there
RAC's response
Thank you. RAC fully agrees with the response provided by the dossier submitter.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany		MemberState	3
Comment received				
In Section 1.2 Table 2 the numerical identifier is missing and the unit of the surface tension should be corrected from nN/m to mN/m. The current Annex VI entry 601-024-00-X is a group entry that encompasses "cumene [1] propylbenzene [2]". In Table 6 of the CLH report, this entry is presented incompletely since propylbenzene is missing. The CLH report does not mention propylbenzene at all. Cumene and propylbenzene are constitutional isomers but two different substances.. Therefore, the current proposal would change the Annex VI entry by deleting the harmonised classification for propylbenzene as the proposed ICI in Table 6 is only refers to cumene. If the current ICI in Table 6 would be kept, then the dossier does not give any evidence why the change of classification is also valid for propylbenzene. This would lead to a situation where there would not be any harmonised classification for propylbenzene at all, since the old index number is used only for the new classification of cumene. A way out of this would be to use a new Index number for the new cumene classification, while the currently used Index Number will only be valid for propylbenzene. In this case, the old group entry would be split and the name cumene needs to be deleted from the ICI of the old entry. To summarize, it is not clear to us, what the target substance of the current CLH proposal is. Is it only cumene or both cumene and propylbenzene, even though the second substance is not addressed in the report? If only cumene is in the focus, should the old harmonised classification be kept for propylbenze or deleted? If the old entry would be modified to only refer to cumene note C should be deleted as it refers to mixtures of isomers, which is not applicable to cumene alone. With regard to the toxicological endpoints only germ cell mutagenicity, carcinogenicity and reproductive toxicity have been assessed in the CLH-Report. There is no statement given why the current classification with Asp. Tox. 1 (H304) and STOT SE 3 (H335) should be maintained. Related to germ cell mutagenicity and reproductive toxicity a non-classification is supported by the German CA since no effects sufficient for classification are reported.				
Dossier Submitter's Response				
The proposed entry 601-024-00-X do included the propylbenzene. This is, as the MS pointed out, not correct. The specific entry will be updated. This proposal for CLH only include isopropylbenzen (cumene) and the Note C in the annex VI will be deleted				

(updated). The Manual Screening was only focused on CMR properties. The exsisting classification will not be discussed or changed and will remain. This dossier only addresses hazard classes which normally are subject to harmonized classification and labelling (Article 36 (1) of the CLP Regulation. Thank you for agreeing to the (non)classification proposal for germ cell mutagenicity and reproductive toxicity
RAC's response
Thank you. RAC agrees with the response provided by the dossier submitter.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	Finland		MemberState	4
Comment received				
Based on the available information cumene has significantly increased lung alveolar/bronchial adenomas/carcinomas in male and female mice, liver adenomas/carcinomas in female mice and nose adenomas in male rats. Cumene-induced lung tumours have more often (87%) K-ras and p53 mutations than spontaneous lung tumours (14%). These type of mutations have also been found in human lung cancer. MoA of liver tumours is unknown and the relevance for humans unclear. Regarding nose adenomas progression to malignancy is unclear. The most relevant data warranting classification of cumene for carcinogenicity is reported in the mice study in which cumene is shown to induce genotoxicity via alterations resembling those found in humans. The proposal is to classify the substance as Carc. 2, however, FI-CA is of the opinion that classification of cumene as Carc. IB, H350 is justified according to criteria of the CLP regulation.				
Dossier Submitter's Response				
Thank you for your comments. As most comments focus on the modes of action of the observed tumour types, an appraisal of the various tumour locations and their possible MoA is given in a separate document ("MoA summary document"), which also contains a short discussion of the mutations found in mice lung tumours and their possible causes. We would like to remark that based on the available information it is difficult to conclude that these mutations were "induced" by cumene (see also response to comment #11).				
RAC's response				
Thank you. RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document".				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	United States	American Chemistry Council	Industry or trade association	5
Comment received				
Please see the attached technical comments on the cumene CLH proposal from the American Chemistry Council's Cumene Panel focusing on mouse liver tumors and our mouse liver pilot study results.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Comments on Cumene CLH Proposal 11 22 19.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ACC Cumene Research Cons Final Int Report Liver Pilot Excerpt.pdf

Dossier Submitter's Response

Thank you for your comments. Your attached documents discuss the possible MoA for the observed liver tumours in mice and provides information from a new mechanistic study. This information has been taken into account in the discussion of MoAs in a separate document ("MoA summary document").

RAC's response

Thank you. RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document".

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	France		MemberState	6

Comment received

Liver tumours in B6C3F1 mice:
Even if we agree that this strain of mice is associated with a high background incidence of liver tumours, the increase of hepatocellular adenoma and carcinoma (combined) is clearly above the historical controls in the study at the highest dose (72% versus NTP HCD = 22-50%). In addition, there is no mechanistic data with cumene for concluding on a role of CAR or PPAR-α-like MoA. Activation of AhR was neither discussed in the CLH report. In this context, the relevance of these tumours should not be discounted.

Renal tumours in F344/N male rats:
In the absence of adequate data for assessing α2microglobuline MoA, all IARC criteria cannot be fulfilled. Thus, the relevance of these tumours should not be discounted. However, because statistical significance was only observed when malignant and benign tumours had been combined, the biological significance of this effect remains uncertain.

Nasal tumours in rats:
In line 3 of section 10.7.1.4, it is noted "[…] adenoma of the respiratory epithelium (including multiple and all sites (0/50, 7/50**, 18/49***, 10/50*** (*** p≤0.001; P for trend: P<0.001)) and in females ((4/50, 31/50***, 42/50***, 46/50***, P for trend: P=0.004)". In contrast, in table 13, incidence for female rats for respiratory epithelium, adenoma was 0/50, 5/48*, 4/50, 3/50. Is there a mistake?

Conclusion: Overall, tumours are observed in 2 sexes (lung tumours in mice) and 2 species (tumours in the lung and liver in mice, tumours in the nose and kidney in rats). This can fulfil with category 1B. We agree that some tumours (especially renal tumour in male rat and liver tumour in mouse) could be associated with a mode of action non-relevant to humans. However, this is only hypothetic since there is no data presented in the CLH report to reach a firm conclusion on the non-relevance of the tumours found. Do you have found any information from ToxCast or QSAR estimation to support the proposal to downgrade into category 2?

Dossier Submitter's Response
Thank you for your comments. A detailed appraisal of the various tumour locations and their possible MoA is given in a separate document ("MoA summary document"). Nasal adenomas in rats: Indeed, there is a mistake in the text in section 10.7.1.4. The incidences as reported in Table 13 are the correct ones. ToxCast/Tox21 was checked for information on CAR agonistic and antagonistic activities of cumene, styrene and ethylbenzene. For all three substances negative conclusions were obtained. Also no interaction with the respective gene, i.e. nuclear receptor subfamily 1 group I member 3 (NR1I3, or CAR, CAR1, MB67) was reported for any of the substances in the Comparative Toxicogenomics Database. So, we don't consider these predictions meaningful for deciding on the MoA.
RAC's response
Thank you. RAC notes that further mechanistic data were provided in pilot study by industry during consultation. Though these data are not sufficient to fully demonstrate this mode of action and to exclude human relevance, it further points towards an involvement of CAR/PXR activation for the observed liver tumours in female mice. RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document".

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawe	Industry or trade association	7
Comment received				
Please see the attached report with our comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONCAWE Cumene Comments 2019.pdf				
Dossier Submitter's Response				
Thank you for your comments, which relate to toxicokinetics and the possible saturation of metabolic pathways (please see response to comment #1), genotoxicity (see response to comments #11 and #12) and the MoAs for various tumour types. An appraisal of the tumour locations and their possible MoA is given in a separate document ("MoA summary document").				
RAC's response				
Thank you. RAC fully agrees with the response provided by the dossier submitter.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Belgium	ReachCentrum on healf of the Phenols & Derivatives Reach Consortium	Industry or trade association	8
Comment received				
The Cumene Registrants do not support classification of cumene as Carc Cat 2, and argue that the data for carcinogenicity, in some cases, do not meet the statistical threshold for				

tumours to be considered increased with treatment, and in all cases, are sufficient to show that tumour induction occurred through modes of action considered irrelevant to humans.
Cytotoxicity is not an integral/essential step in the CYP2F2-mediated MoA for lung tumours, for which a primarily mitogenic driver has been shown. Although a specific and detailed MoA dataset is lacking for cumene, this MoA is supported by read-across to the more extensive MoA investigations available for ethylbenzene and styrene. The latter substances are related alkylbenzenes that exhibit similar tumour profiles as cumene. The CYP2F2-mediated MoA for lung tumour development is irrelevant to humans; thus, these tumours cannot serve as a basis for the cancer classification of cumene.
Liver tumours are common in B6C3F1 mice, and when appropriately assessed for statistical significance using more stringent thresholds to avoid unreasonable false positive tumour detection ($p<0.01$ for pair-wise comparisons and $p<0.005$ for trend tests; OECD TG 116), are not statistically significantly increased in female mice. Further, sufficient data are available or in process (pilot study) for cumene to show that these tumours, if related to treatment, are mediated through a CAR MoA. Because the CAR-mediated MoA is irrelevant to humans, the liver tumours should not serve as a basis for the cancer classification of cumene.
Renal tumours are common in male F344/N rats and do not meet the analytical threshold ($p<0.01$ for pair-wise comparisons and $p<0.005$ for trend tests; OECD TG 116) to be considered statistically significantly increased with cumene treatment. Further, sufficient essential and supporting data are available to show that these tumours occur through an α2u-globulin MoA. Because the α2u-globulin MoA is irrelevant to humans, these tumours cannot serve as a basis for the cancer classification of cumene.
No malignant neoplasms of the nasal respiratory epithelium developed after two years of high dose exposure, supporting the lack of progression to malignancy. Further, the data show a role for CYP2F in the MoA for cumene-induced rat nasal tumours. Because the CYP2F-mediated MoA is not relevant to humans, these tumours cannot serve as a basis for the classification of cumene for carcinogenicity.
Other rat and mouse tumour endpoints following chronic cumene exposure were within known spontaneous background ranges and/or did not meet the statistical threshold relevant to common tumours. Thus, these other tumour data should provide no weight in the overall assessment for cancer classification.
Overall, the tumour types observed in the cumene studies do not provide a reliable or adequate basis for classification. Most importantly, none of the MoAs for these tumours are relevant to humans. No classification should be applied.
Comments address Sections 10.7.1.1 (p. 36-39), 10.7.1.2 (p. 39-40), 10.7.1.3 (p. 40-41), 10.7.1.4 (p. 42), 10.7.1.5 (p. 42), 10.7.2 (p. 45-47) and 10.7.3 (p. 47-48) of the CLH proposal.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cumene_PandD-Cons_Carcinogenicity_November 2019.zip

Dossier Submitter's Response

Thank you for your comments. For a detailed response on possible MoAs for the various tumour sites please see the separate document provided ("MoA summary document"). With regard to cytotoxicity Cruzan *et al.* 2018 is considering both cytotoxicity and mitogenicity as possible mechanisms: "Key event 3 is driven primarily by mitogenicity (stimulation of cell proliferation by ring-oxidized metabolites) with the possibility of weak cytotoxicity as evidenced by increased cell debris and enzyme biomarkers in lung lavage fluids." The metabolite 4-hydroxystyrene is discussed by the authors as the toxic metabolite responsible for the toxic effects on Clara cells. The critical point is to show that proliferation is depending on metabolism by CYP2F2 (see discussion in separate

document).

Statistical evaluation of liver tumours in mice:
There is a clear trend towards increased tumour incidences with higher concentrations for female mice, but the differences to controls are modest and reach the $p<0.05$ level only for the highest dose group. With a more strict criterion of $p<0.01$ the increase would not be statistically significant, but the incidence for adenoma and carcinoma combined in the highest dose group was clearly above the range of historical controls. Statistical significance is only one aspect when evaluating study findings and the borderline significance is taken into account in the interpretation of the data.

Statistical evaluation of renal tumours in male rats:
The statistical evaluation as performed by NTP (2009) was reported in the CLH dossier. While it is correct that the increase in the combined incidence of adenoma and carcinoma of the renal tube just met the statistical criterion of $p<0.05$ ($p=0.044$ in 500 ppm group) and according to the OECD Guidance Document 116 also a p value of 0.01 could be applied, induction of hyperplasia (considered to be a precursor) was highly significant at the $p<0.01$ level and therefore the renal tube observed should be considered treatment-related. In addition, incidences in exposure groups clearly exceeded historical control ranges.

RAC's response

Thank you.
Regarding the observed lung tumours in mice RAC is of the view that the postulated MoA with involvement of CYP2F2 metabolism in Clara cells is not fully supported by the available mechanistic studies. The lack of cytotoxicity clearly is in contradiction with this MoA. Structural similarity to substances for which this MoA was confirmed (e.g. styrene) is no sufficient to assume that the same MoA is active for cumene as well (in line with US EPA, 2014 and Pandiri, 2015). In addition, Clara cell loss was described for styren exposure, but was not seen with cumene nor with the closely related substance ethylbenzene.
Ring hydroxylation seems to be a rather minor route for the metabolism of cumene and no quantitative difference was demonstrated for mice and rats, where no lung tumours were observed.
A combination of more than one mode of action is likely to be the cause for the observed lung tumours. Despite the relatively high background incidence of lung tumours there was a very strong and statistically significant increase in this tumours type in male and female mice. Moreover, the increase was clearly above historical control range values.
RAC agrees that there was only a weak statistically significant increase in liver tumours in female mice, which was however above HCDs at all tested doses. Overall, the weight of this tumour type is not considered high in the weight of evidence analysis. In addition there are indications for a CAR mediated MoA, which was however, not sufficiently investigated.
RAC agrees with the dossier submitters conclusion that the renal tumours were treatment related, which is also supported by the statistically significant increase in renal tube hyperplasia and that historical controls were exceeded in all dose groups.

In conclusion RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document".

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CUMENE

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	United States		Individual	9

Comment received

We do not support classification of cumene as Carc Cat 2.

The lack of a cancer classification decision is warranted based on both statistical and MoA considerations as follows:
1) Tumour responses are weak and do not achieve statistical significance using the Haseman rule (Haseman 1983, 1984; OECD 2012) for statistical evaluation of common (> 1% incidence) animal tumours (female mouse liver and male rat kidney);
2) CAR receptor activation, a MoA not regarded as human relevant, is supported by the pattern of P450 and genomic responses in cumene-treated mice and is consistent with the low increase of liver tumours in cumene-treated female mice.
3) A mouse lung-specific CYP2F2-mediated MoA, which is not regarded as qualitatively or quantitatively relevant to humans, is supported for cumene's mouse lung-specific tumorigenicity by the nature of the mouse lung-specific tumour response and read-across to CYP2F2 MoA data derived from the close structural analogs, styrene, styrene oxide and ethylbenzene.
4) Criteria identifying an α2u-globulin MoA, which is not regarded as qualitatively relevant to humans, are adequately fulfilled with cumene-specific data for the cumene-induced male rat kidney tumours.
5) A hypothesized CYP2F-mediated MoA, coupled with observation that cumene-induced rat nasal tumours were observed at study termination and had not progressed to malignant carcinomas, indicating that this tissue response does not inform the overall carcinogenicity of cumene.
Other rat/mouse tumour endpoints following chronic cumene exposure were within known spontaneous background ranges and/or did not meet the statistical threshold relevant to common tumours, and thus, provide no weight in the overall assessment for cancer classification.
For all of the above-proposed tumour MoAs, the overall CLH genotoxicity conclusion indicates that a genotoxic MoA is not plausible for cumene. Most importantly, none of the MoAs proposed for these tumours are relevant to humans. No classification should be applied.

Haseman JK. 1983. Statistical support of the proposed National Toxicology Program protocol. Toxicologic Pathology 1:77-82.

Haseman JK. 1984. Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environmental Health Perspectives 58:385-392.

Organisation for Economic Cooperation and Development (OECD). 2012. Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Testing Guidelines 451, 452 and 453. ENV/JM/MONO(2011)47. 13 April 2012.

Comments address Sections 10.7.1.1 (p. 36-39), 10.7.1.2 (p. 39-40), 10.7.1.3 (p. 40-41), 10.7.1.4 (p. 42), 10.7.1.5 (p. 42), 10.7.2 (p. 45-47) and 10.7.3 (p. 47-48) of the CLH proposal.

Dossier Submitter's Response

Thank you for your comments. Regarding statistical interpretation we would like to refer to our response to comment #8. A discussion of MoAs for various tumor sites is provided in a separate document ("MoA summary document").

RAC's response
Thank you. Also RAC would like to refer to its response to comment #8. In addition, RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document".

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany		MemberState	10

Comment received

The proposed classification as carcinogen is supported by the DE CA, and the evidence is clearly explained.

Neoplastic lesions are observed (with significance compared to control animals) in chronic inhalation studies in mice and rats (NTP):
• lung (adenoma and carcinoma) in male and female mice,
• liver (adenoma) in female mice,
• haemangiosarcoma of spleen in male mice,
• nose (RE adenoma, OE hyperplasia only) in rats,
• kidney (adenoma and carcinoma) in male rats and
• testis (adenoma) in male rats.

Based on these results, DK comes to the conclusion (p. 45) that overall there is sufficient evidence in animals for carcinogenicity. This evaluation corresponds with the assessment by IARC ("sufficient evidence") and the conclusion of the NTP report ("clear evidence for carcinogenic activity" in mice and male rats, "some evidence" in female rats). Without consideration of confounding factors, according to the CLP guidance this would result in a category 1B classification.

It is argued on p. 45, that the relevance for humans of the findings in test animals is seriously questioned. A discussion of particular tumours and their relevance for humans is presented in section 10.7.1 (pp. 36) of the CLH report, but human relevance cannot be clearly excluded for any of the neoplastic lesions:
• For lung tumours in mice,
o genotoxicity cannot be excluded (p. 37),
o many genes with altered expression in the mouse tumour model may play a role in human lung and other cancer (p. 38),
o there is insufficient evidence for a presumed CYP 2F2 dependence and significant concerns remain for human relevance.
• For liver tumours in female mice, there are no data available to link cumene to either a CAR- or PPARa-like MoA (p. 40). The authors conclude that induction of liver tumours is uncertain with respect to human relevance.
• For renal tumours in male rats (p. 41), a2u-globulin accumulation seems to be likely; however, NTP concludes that it cannot be ruled out that other mechanisms such as genotoxicity also contribute to kidney tumour formation. The authors of the CLH report adopt the NTP conclusion that human relevance is uncertain.
• For the nasal tumours in rats, relevance for humans cannot be excluded (p. 42).

Taken together, the human relevance of the results might be debateable, but there is no data presented for any of the observed neoplastic lesions that is sufficient to support a MoA, that is clearly not relevant for humans. The proposed but not substantiated lack of human relevance can therefore not be used as main argument for Cat. 2 versus 1B. The

evidence presented rather explains, why non-classification because of lack of human relevance should not be considered.

There are additional factors that need to be taken into account for a conclusion on categorisation in either 1B or 2, e.g.:
• statistically significant increased incidences of malignant tumours are found in one species (treatment related);
• most neoplastic lesions were benign (e.g. adenomas);
• progression to malignancy cannot be excluded;
• tumours occur in both species and sexes treatment related;
• multi-site response in both species;
• species dependency of tumour sites;
• some tumours did not show a dose-response-relationship;
• two tumour types are mentioned in the guidance as tumour types with high spontaneous tumour incidence (liver tumours in B6C3F1 mice, Leydig (=interstitial) cell adenomas in male F344 rats).

A major argument for a classification as Category 2 in the dossier is based on uncertain human relevance: On p. 47: "The relevance of the observed tumours in experimental animals is uncertain (less than sufficient evidence), which would be needed for classification in Category 1B." This is in contrast to the CLP legislation, which assumes human relevance of findings in animal experiments "unless there is strong evidence that the mechanism of tumour formation is not relevant for humans" (CLP Regulation, Annex I: 3.6.1.1.). The argumentation in the dossier for categorization should therefore be based on weighing the pros and cons of the findings in the animal studies for categorization into Cat. 1B or 2. A (tabular) comparison of arguments in favour or against Cat. 1B or 2 would be highly supportive.

Further comments:
It should be at least discussed (better calculated) whether setting a specific concentration limit needs to be considered or whether the GCL should be used.

Although available studies do not suggest a genotoxic mode of action, it cannot be excluded based on available data. It should be discussed, whether a threshold can be assumed for cumene.

Dossier Submitter's Response

Thank you for your comments. A discussion of MoAs for various tumor sites is provided in a separate document ("MoA summary document"), where we took up your suggestion to provide a tabular overview of arguments pro/contra specific MoAs. Your question regarding a potential threshold for carcinogenic effects is addressed together with the MoA for lung tumours in mice. As there is a high uncertainty about the MoA no threshold can be derived.

According to the guidelines for setting SCL (EC, 1999) the carcinogenic potency of cumene can be determined based on the data presented by NTP (2009) on alveolar/bronchiolar adenoma or carcinoma in male and female mice after inhalation exposure. The T25 was calculated for both sexes and transformed in a body dose as outlined on page 9 and 10 of the guideline (using the inhalation volume of 1.8 L/h). The resulting T25 value is > 100 mg/kg bw x d for male and female animals (128 mg/kg bw x d and 161 mg/kg bw x d, resp.). In the potency evaluation this leads to the low potency group. When applying an inhalation volume as suggested in the document submitted by the Phenol&Derivative REACH Consortium (54.2 ml/min = 3.25 L/h) an even higher T25

value is calculated. This T25 value leads to the same group of low potency.

RAC's response

Thank you. RAC broadly agrees with the dossier submitter's interpretation of the different modes of action relevant for cumene as provided in the separate document "MoA summary document". In line with the dossier submitter, RAC is of the view that the presented uncertainties with regard to the underlying cause(s) of the lung tumours does not allow the derivation of a possible threshold for this tumour type.

Based on the alveolar/bronchiolar adenoma or carcinoma observed in male and female mice, RAC calculated the following T25 values, based on the EC (1999) guidance document.
Using the inhalation volume for mice as recommended in EC (1999), i.e. 1,8 l/h, the T25 for males was 210 mg/kg bw/day ➔ > 100 mg/kg bw/day ➔ low potency group, but for females a T25 of 88,6 mg/kg bw/day was calculated, which as it is below 100 mg/kg bw/day points towards the medium potency group.

However, when using the inhalation volume of 3,25 l/h, as recommended in the document submitted by the Phenol&Derivative REACH Consortium, higher T25 values are achieved.

The value of 3,25 l/h for the inhalation volume appears superior to the default value recommended in EC (1999), as it is based on plethysmograph measurements in unanaesthetised mice of the relevant strain, i.e. B6C3F1 (US EPA, 1988).

Males: T25 of 379 mg/kg bw/day ➔ > 100 mg/kg bw/day ➔ low potency group

Females: T25 = 160 mg/kg bw/day ➔ > 100 mg/kg bw/day ➔ low potency group

The derived T25 values support the introduction of SCLs higher than the GCLs for cumene according to the CLP guidance.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Belgium	ReachCentrum on behalf of the Phenols & Derivatives Reach Consortium	Industry or trade association	11

Comment received

The Cumene Registrants agree that no classification for mutagenicity is required for cumene.
The mutagenic, clastogenic, and aneugenic properties of cumene have been adequately investigated both *in vitro* and *in vivo*. However, the CLH proposal is unbalanced in that it provides a limited summary of the large body of negative evidence for genotoxicity compared to the more detailed discussion afforded to the spurious positive findings. Further, the few positive genotoxicity findings discussed in the CLH proposal are generally based on outdated/unvalidated/unreliable methods or extrapolated from minor metabolites of cumene. The SCE assay is no longer considered a bona fide genotoxicity endpoint and should be afforded little to no weight in the overall analysis. The positive mutation assay of AMS-oxide is in contrast to the overwhelmingly negative data available

for the cumene and AMS; further, the preponderance of evidence supports the conclusion that cumene is not an *in vivo* clastogen/aneugen. Finally, the higher frequency of K-ras and p53 mutations in lung tumours from cumene-exposed mice compared to controls is more likely a molecular change of effect (increased cell proliferation) rather than a cause. Importantly, despite the overall CLH conclusion that cumene is not a genotoxicant, MoAs related to genotoxicity are not appropriately excluded in the CLH proposal when addressing primary tumour endpoints of concern.
Comments address Sections 10.6.1 (p. 27-29), 10.6.2 (p. 29-30), 10.6.3 (p. 30), 10.7.1.1.a and b (p. 37-38), 10.7.1.2.a (p. 39), and 10.7.1.3.a (p.41) of the CLH proposal.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cumene_PandD-Cons_Carcinogenicity_November 2019.zip

Dossier Submitter's Response

Thank you for your comment. We consider it the dossier submitter's obligation to report all available data which could be relevant for a conclusion on classification. This sometimes implies reporting of older, outdated or unvalidated studies. It even implies the reporting on unreliable studies (reliability 3 or 4), if these data are mentioned elsewhere or cover an endpoint not covered by other (reliable) studies. The dossier is the basis for RAC´s conclusion on classification; it should contain all information necessary to allow an independent decision making and therefore, especially the positive results, have to be discussed in detail. This may lead to the impression that the CLH proposal is unbalanced. However, as the commentator can see, in the final conclusion the dossier submitter decided on the proposal of non-classification for the endpoint germ cell mutagenicity.

For clarification of the NTP (2013) statement "these molecular changes may be an effect rather than a cause" it needs to be mentioned that NTP further elaborates "The high frequency of K-ras mutations in adenomas (4 of 6) suggest that K-ras activation was a relatively early event and occurred either prior to or during this benign stage of carcinogenesis; however, the sample size was small (only 6 of 191 adenomas were examined for ras mutations)" and
"Cumene-induced mouse lung tumors have more K-ras and/or p53 mutations than do spontaneous lung tumors. Furthermore, the mutational spectra of K-ras and p53 in lung tumors from mice exposed to cumene differ from those observed in spontaneous lung tumors. These findings suggest the involvement of DNA damage (either direct damage from adduct formation or indirect damage through reactive oxygen species) and genomic instability. The K-ras and p53 mutations observed in cumene-induced lung tumors were accompanied by increased expression of genes involved in the alteration of the mitogen-activated kinase signaling pathway, invasion and metastasis, inhibition of apoptosis, increased angiogenesis, and increased metastatic potential. These molecular alterations resemble those found in human lung and other cancers."
In conclusion, how these molecular changes were induced is unknown and none of the possibilities can be ruled out completely. Please see also the summary on the evidence for possible MoA in the separate document ("MoA summary document").

RAC's response

Thank you for your comment.

Several major points were raised in your comment (detailed in the public attachment) and are addressed here.

Unbalanced data
RAC agrees with DS's response on the necessity to have in the CLH dossier all available data which could be relevant for a conclusion on classification.
RAC also considered that the discussion provided by the DS was not unbalanced. Discussion on both negative and positive results and caveats regarding these findings is warranted for an overall WOE analysis.

Positive findings observed in Tardiff *et al.*, 1975
RAC agrees that the positive findings observed in the spot test in bacteria (Tardiff *et al.*, 1975) is of negligible weight as compare to the six negative Ames assays. RAC agrees that cumene did not induce gene mutation in bacteria. Regards gene mutation in mammalian cells, RAC disagrees that cumene was largely negative in the *in vitro* mammalian genotoxicity data available. The two available studies had major caveats that clearly raised concern on their reliability. RAC agrees that cumene was negative for cytogenicity in mammalian cells in presence or absence of metabolic activation although some limitations were noted in the available study. The UDS test is considered of low weight.

AMS genotoxicity
RAC agrees that the *in vitro* weakly positive SCE assay should have a lower weight than the negative *in vitro* chromosome aberration assay on AMS. Nevertheless, RAC would like to point out the following unresolved issues on AMS genotoxicity:

- no *in vitro* gene mutation assay on mammalian cells or *in vivo* comet assay were available for AMS. The gene mutation potential of AMS has not been fully investigated. Positive findings observed in the Ames assay for AMS metabolite AMS oxide also raised issues on the potential of AMS to induce gene mutation.
- *In vivo*, inconclusive results were obtained in the NTP study with sub-chronic exposure (positive in females and negative in males). The negative results in the *in vivo* single administration study in males (Rim, 2012) does not fully clarify the positive findings.

***In vivo* clastogenicity/aneugenicity of cumene**
RAC agrees that the positive results obtained following intraperitoneal route of exposure in the micronucleus assay is of low weight compare to the three negative studies using relevant route of human exposure (oral, inhalation). Overall, cumene did not induce damage at chromosomal levels in rats and mice *in vivo* at relevant route of exposure. Nevertheless*, as elaborated in the guidance on application of the CLP criteria "A positive result for somatic or germinal mutagenicity in a test using intraperitoneal administration only shows that the tested substance has an intrinsic mutagenic property, and the fact that negative results are exhibited by other routes of dosage may be related to factors influencing the distribution/metabolism of the substance which may be characteristic to the tested animal species."*

Small increase in the comet assay and background variation
RAC agrees that the main limit of the available *in vivo* comet assay is the absence of historical negative control data. Although some variability in the results were observed in mice lung, no such variation was noted in liver. Moreover, there are no data suggesting that the concurrent negative controls would not be appropriate.

Flare assay (Kim, 2008)
RAC agrees that the results of the Flare assay are unreliable to study deficiencies.

***K-ras* and *p53* mutation in tumours**
RAC agrees with the DS's response pointing out the NTP (2013). RAC also agrees with the DS's response: how these molecular changes were induced is unknown and none of the possibilities can be ruled out completely.

Conclusion on germ cell mutagenicity classification
Overall, RAC is of the opinion that cumene was able to induce DNA damage and gene mutation *in vivo* in somatic cells. Whether the positive findings observed in the studies fulfilled the CLP criteria for classification as germ cell mutagen needs to be discuss at RAC meeting.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawe	Industry or trade association	12
Comment received				
Please see the attached report with our comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONCAWE Cumene Comments 2019.pdf				
Dossier Submitter's Response				
Thank you for your comment. The positive *in vivo* micronucleus test with i.p. application is mentioned in parallel to four negative *in vivo* micronucleus tests with oral or inhalation exposure. As noted in the comment, the FLARE assay is a not a validated test method to assess genotoxicity. This is one of the reasons why a reliability of 4 was given to the study of Kim *et al.* (2008). As explained in the response to comment # 11 it is the dossier submitter's obligation to report relevant studies as complete as possible, including those of low reliability, if their discussion is necessary to establish the full picture. In your comment you state: "While the report did indicate that the observed changes may be an effect rather than a cause of the multistage carcinogenic process, this observation is expected considering the observed alveolar metaplasia and hyperplasia; in such rapidly dividing tissues, mutations are more likely. Therefore, these observations are a resulting effect and not a cause". With regard to the relevance of the k-ras and p53 mutations we refer to our response to comment #11.				
RAC's response				
Thank you for your comment. Please refer to our response to comment #11				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CUMENE

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	United States		Individual	13
Comment received				
We agree that no classification for mutagenicity is required for cumene. The *in vitro* and *in vivo* mutagenic, clastogenic, and aneugenic properties of cumene have been adequately investigated. However, the CLH proposal is unbalanced in that it provides a limited summary of the large body of negative evidence for genotoxicity. The SCE assay is no longer considered a bona fide genotoxicity endpoint. The positive mutation assay of AMS-oxide contrasts with the overwhelmingly negative data for cumene and its minor metabolite AMS. The higher frequency of K-ras and p53 mutations observed in terminal lung tumours from cumene-exposed mice compared to controls do not inform early key events (mutagenic or otherwise) responsible for the MoA of cumene-induced tumorigenicity. The overall CLH conclusion is that cumene is not classifiable as either a Cat 1 or 2 mutagen. However, the CLH evaluations of the tumour MoAs all conclude that genotoxicity/mutagenicity cannot be excluded. This inconsistency with the primary CLH classification recommendation regarding mutagenicity is not acceptable. Comments address Sections 10.6.1 (p. 27-29), 10.6.2 (p. 29-30), 10.6.3 (p. 30), 10.7.1.1.a and b (p. 37-38), 10.7.1.2.a (p. 39), and 10.7.1.3.a (p.41) of the CLH proposal.				
Dossier Submitter's Response				
Thank you for your comment. Please see response to comment #11. We would like to remind that the classification for M refers to inheritable germ cell mutagenicity. Although based on the existing evidence the proposal for this endpoint is non-classification this does not eliminate all remaining uncertainties for a genotoxic MoA for somatic cell carcinogenicity.				
RAC's response				
Thank you for your comment. Please see response to comment #11.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2019	United Kingdom		Individual	14
Comment received				
Comments on mutagenicity in attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Fowler Cumene review 0028.pdf				
Dossier Submitter's Response				
Thank you for your comment and detailed evaluations. Indeed, the NTP database indicates only one additional Comet assay (for styrene-acrylonitrile trimer) which was performed in Fisher rats. In this assay 5 male and 5 female rats per dose group were used. The individual animal data show that in the control group mean %tail DNA was between 5.3% and 9.6% for effects observed in the liver of males. One animal in the control group showed a very high value of 21.9%. This is reflected in the mean value of				

10.605 ± 2.951 %tail DNA reported for the control group. The high variability observed in the controls of this second study gave raise to some doubts regarding the reliability of the results observed in the cumene comet assay. Nevertheless, a dose-response relationship was observed and the Comet assay on cumene was performed with a sufficient number of animals (six/sex/dose). The OECD test guideline 489 (*In vivo* mammalian Alkaline Comet Assay) specifies the use of "*a minimum of 5 analysable animals of one sex or of each sex if both are used*". So, there is some uncertainty about the results, but the test cannot be completely ignored for evaluation of genotoxic properties of cumene.

Regarding the genotoxicity of α-methylstyrene, the weakly positive result in the high dose group was already addressed by the dossier submitter by mentioning "significance uncertain" in Table 11.
Formation of reactive oxygen species (ROS) is discussed by the commentator as a possible MoA. There is no study available providing evidence for generation of ROS in male and female mice after cumene exposure. In the FLARE assay, which can be applied to investigate DNA damage from reactive oxygen species, no clear duration-response relationship was observed and the study is qualified as being insufficient in reporting of methods and results. In conclusion, we do not consider this study as convincing evidence for a ROS-mediated MoA. For further details see the separate document ("MoA summary document").

RAC's response

Thank you for your comment and in-depth analysis of the comet assay (including individual values), AMS genotoxicity and Kras and p53 mutation induced lung tumours.

Comet assay
In the other provided NTP experiment provided with F344 juvenil rats, RAC notes that DNA background may differ between F344 young adult rats used in the cumene study (8-weeks of age). Moreover, the high variability observed in the styrene-acrylonitrile trimer study (individual values between 5.3 and 21.9%) was not observed in the case of cumene.
RAC agrees that in lung, variability cannot be excluded. Nevertheless, the increase was dose-related and a strong association ($p<0.01$) was noted at the top dose suggesting that the results may not only be due to background variations in the results.

AMS genotoxicity
Thank you for the detailed results provided on the *in vivo* assay performed on AMS. RAC acknowledge that the absence of historical range is a limitation in the interpretation of the *in vivo* micronucleus study and that hypoxia cannot be completely ruled out. Nevertheless RAC considered the study as the DS, inconclusive. RAC also noted that the proposed hypothesis of a non-direct MoA for AMS is not substanciated by data on AMS.

Kras and p53 mutation
RAC acknowledge that DNA damage observed in lung tumours could be due to a consequence of irritation combined with inflammation leading to ROS. Nevertheless, although the authors of the studies found mutation suggestion DNA damage via ROS generation, it may be noted that other type of mutations were found. Please see also response to comment #11 on this subject.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CUMENE

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	France		MemberState	15

Comment received

Based on the data available, it is not clear why the NTP studies (2007 – with methyl styrene; 2009 & 2012 – with cumene) on bacteria are not judged of adequate reliability (reliability 3 noted in the table)?

Could you please specify if cytotoxicity was measured in the NTP (2012) comet study in order to differentiate genotoxicity to cytotoxicity?

Positive results are reported in the NTP (2009) study (micronucleus assay by ip route). This study should be more deeply discussed in the comparison with CLP criteria. Indeed, as cited in the CLP guidance (page 367), in some cases, a classification as category 2 may be applied if only intraperitoneal *in vivo* tests show mutagenicity/ genotoxicity.

"[…] However, it also has to be taken into account that there is generally no threshold for mutagenicity unless there is specific proof for the existence of such a threshold as may be the case for aneugens. Thus, if mutagenicity/genotoxicity can only be demonstrated for the intraperitoneal route exclusively, then this may mean that the effect in the *in vivo* tests using application routes other than intraperitoneal may have been present, but it may not have been detected because it was below the detection limit of the oral, dermal, or inhalation test assays." (CLP guidance, 2017)

Dossier Submitter's Response

Thank you for your comment.
1) According to the OECD TG 471 (Bacterial Reverse Mutation Test) five different bacterial strain have to be used for an Ames test: S. typhimurium TA 1535; TA 1537 or TA 97 or TA 97a; TA 98; TA 100 and E.coli WP2 uvrA or WP2 uvrA (pKM101) or S. typhimurium TA102. In all NTP studies mentioned in the comment (NTP 2007, 2009 and 2012) at least one of these requested strains was not tested. Therefore a reliability of 3 was assigned.

2) NTP (2012) does not provide any information on cytotoxicity in their comet assay.

3) The CLP guidance points out: If there are positive results in at least one valid *in vivo* mutagenicity test using intraperitoneal application, or from at least one valid *in vivo* genotoxicity test using intraperitoneal application plus supportive *in vitro* data, classification is warranted. In cases where there are additional data from further *in vivo* tests with oral, dermal or inhalative substance application, a weight of evidence approach using expert judgement has to be applied in order to come to a decision.

The positive result obtained in the *in vivo* micronucleus study (genotoxicity study, NTP 2009) after i.p. application was found to be in contrast to clearly negative findings with cumene in *in vitro* studies. In a more recent assessment, cumene was negative in a *in vivo* micronucleus study with gavage application in male F344/DuCrl rats (NTP, 2012). Further tests on micronuclei with mice (B6C3F1, Swiss) with gavage or inhalation exposure also provided negative results. In a weight of evidence approach it was concluded that a classification based on the positive result of the i.p. study did not seem justified.

RAC's response
Thank you for your comment. RAC agrees that the positive results obtained following intraperitoneal route of exposure in the micronucleus assay may indicate an intrinsic potential of the substance. Nevertheless, cumene did not induce damage at chromosomal levels *in vitro* or *in vivo* in rats and mice at two relevant route of exposure (gavage and inhalation). Thus, RAC considered that more weight should be given to the negative micronucleus studies performed according to relevant route of exposure.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Belgium	ReachCentrum on healf of the Phenols & Derivatives Reach Consortium	Industry or trade association	16

Comment received
We concur with the CLH report that the developmental and reproductive data for cumene are insufficient to classify the compound as a reproductive toxicant. Comments address Sections 10.8.2 (p. 52), 10.8.3 (p. 52-53), 10.8.5 (p. 55), 10.8.10 (p. 55-56) of the CLH proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cumene_PandD-Cons_Carcinogenicity_November 2019.zip
Dossier Submitter's Response
Thank you for your comment. In the NTP report it is stated that for male mice l. cauda epididymis weight in the 3 month study in control animals was 0.0196 g ± 0.0010 g and in the highest concentration group 0.0171 g ± 0.0006 g* (significantly different (P≤0.05) from the chamber control group, see page 171 of the 2009 document). Whole l. epididymis weight was not significantly different in any concentration group compared to control. Necroscopy body weight in the control group was 38.3 g ± 0.7 g and 34.7 g ± 0.6 g** in the high concentration group (significantly different (P≤0.01) from the chamber control group). Based on these data we agree with the commentator that these data are an equivocal indicator for male mouse reproductive toxicity.
RAC's response
Thank you. RAC agrees with the dossier submitter's response.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawe	Industry or trade association	17

Comment received
Please see the attached report with our comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONCAWE Cumene Comments 2019.pdf

Dossier Submitter's Response
Thank you for your comment. Please refer to comment #16 for the dossier submitter's answer.
RAC's response
Thank you. RAC agrees with the dossier submitter's response to comment #16.

Date	Country	Organisation	Type of Organisation	Comment number
20.11.2019	United States		Individual	18
Comment received				
We concur with the CLH report that the developmental and reproductive data for cumene are insufficient to classify the compound as a reproductive toxicant. Comments address Sections 10.8.2 (p. 52), 10.8.3 (p. 52-53), 10.8.5 (p. 55), 10.8.10 (p. 55-56) of the CLH proposal.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	France		MemberState	19
Comment received				
Fertility: In the absence of adequate fertility study and considering the current data (only 90 day inhalation studies available), the overall information should rather be considered as inconclusive and insufficient to conclude on classification for fertility.				
Dossier Submitter's Response				
Thank you for your comment. The non-classification for the endpoint "adverse effects on sexual function and fertility" was based on two reliable 90d inhalation studies in rats and mice by NTP from 2009. In these studies reproductive organs were examined histologically, weight of reproductive organs, spermatid parameters, epididymal spermatozoal parameters as well as female oestrous stages were determined. In addition, results from an older 13 week inhalation study in male and female rats examined effects of cumene on spermatogenesis and ovary weight. However, neither a reproduction screening study nor a one-generation study is available for the substance. We agree that there is a lack of specific studies for the endpoint sexual function and fertility, which might lead to the conclusion "*data lacking"*.				
RAC's response				
Thank you. RAC agrees that there is lack of data with regard to fertility. The observed findings in the 90 day NTP-study (i.e. reduced epididymal weight and reduced spermatid count in the cauda epididymis in male mice of the top dose only; increased time in oestrus without dose response, no impact on lengthening of the cycle or acyclicity and no histopathological findings in the ovary in female rat) are considered not sufficient to support a classification.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CUMENE

PUBLIC ATTACHMENTS
1. ACC Comments on Cumene CLH Proposal 11 22 19.pdf [Please refer to comment No. 5]
2. CONCAWE Cumene Comments 2019.pdf [Please refer to comment No. 7, 12, 17]
3. Cumene_PandD-Cons_Carcinogenicity_November 2019.zip [Please refer to comment No. 1, 8, 11, 16]
4. Fowler Cumene review 0028.pdf [Please refer to comment No. 14]

CONFIDENTIAL ATTACHMENTS
1. ACC Cumene Research Cons Final Int Report Liver Pilot Excerpt.pdf [Please refer to comment No. 5]

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