COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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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Substance name: cumene
CAS number: 98-82-8
EC number: 202-704-5
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				

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.

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.				

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.

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				

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?

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawwe	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				

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

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.

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.

MUTAGENICITY

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	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

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawwe	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				

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.

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				

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 inhalative test assays." (CLP guidance, 2017)				

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

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Belgium	Concawwe	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				

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.				

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 unconclusive and insufficient to conclude on classification for fertility.				

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]