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: 2-(4-tert-butylbenzyl) propionaldehyde
CAS number: 80-54-6
EC number: 201-289-8

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.12.2013	France		MemberState	1
Comment received				
More details should be provided, and tables for clear views of the effects depicted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	Belgium	Procter & Gamble Corporation	Company-Downstream user	2
Comment received				
☐ We support the proposal for a harmonized classification of LYSMERAL, CAS# 80-54-6; EC# 201-289-8, as CMR Repro Cat 2 (H361f: Suspected of damaging fertility). The supporting arguments are provided below under Reproductive Toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	United States	Firmenich SA	Company-Downstream user	3
Comment received				
Sufficient toxicology data exists supporting the current hazard assessment and proposed classification of Lysmeral as CMR2.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	Switzerland	Coty Geneva SA	Company-Downstream user	4
Comment received				
We support the classification 2-(4-tert-butylbenzyl) propionaldehyde as CMR2. It has enough data on reproductive toxicity to be classified as CMR2. The data support the dermal exposure with no reproductive effects. Reproductive toxicity seen in male rats has lower significance to humans because 1) toxic effects indicate a well-defined threshold effect; the exposure to humans is far below this limit and 2) toxic metabolite is seen at significantly lower levels in humans than in rats 2-(4-tert-butylbenzyl) propionaldehyde is used in our cosmetic finished goods. There is no intention to ingestion. The exposure is dermal. The assessment should be based on dermal				

exposure. The safe use of it is also demonstrated in the currently under review SCCS dossier.

All restrictions of the IFRA classes are respected in all our finished products since years. No case of adverse effect or consumer concern has ever been reported to our company.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	United Kingdom	Givaudan UK	Company-Importer	5

Comment received

This substance is used only in fragrances for cosmetic and household care products where exposure to the skin is the most relevant route of exposure for workers and consumers. It is not intended for use in products with the potential for oral ingestion.

The data in the dossier support that no reproductive effects would be seen via the dermal route of exposure. Furthermore, reproductive effects seen in the male rat has low relevance to humans because 1) a toxic metabolite was seen at significantly lower levels in humans than in rats 2) toxic effects showed a clear threshold effect and human exposure is well below this threshold.

BMHCA is a sensitizer and labelled as R43. For many years an IFRA Standard has been in place that restricts the use of this material in consumer products. The allowed maximum values are far lower than the no effect levels derived from animal studies.

An SCCS dossier for safe use approval in cosmetics has been submitted and is currently under evaluation. The Margin of Safety is well above 100, which provides sufficient evidence for the safe use of this material.

In conclusion, the extensive data and studies on reproductive toxicity are considered satisfactory for hazard assessment and are sufficiently scientifically rigourous to classify BMHCA as CMR2.

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2013	France	CHARABOT	Company-Downstream user	6

Comment received

Lismeral/Lilial is exclusively used in fragrances for cosmetic and household care products where skin exposure is the most relevant route of exposure to both consumers and workers. No use in products with potential for ingestion.
Lysmeral/Lilial is a known sensitizer and labeled as R43. Since many years an IFRA Standard exists which restricts the use of this material in consumer products. The allowed maximum values are by far much lower than the no effect levels derived from the animal studies.
A SCCS dossier for safe use approval in cosmetics has been submitted and is currently under evaluation. The Margin of Safety is well above 100, which provides sufficient evidence for the safe use of the material.

Date	Country	Organisation	Type of Organisation	Comment

				number
11.12.2013	France	ROBERTET S.A.	Company-Downstream user	7
Comment received				
This substance is exclusively used in fragrances for cosmetic and household care products where skin exposure is the most relevant route of exposure to both consumers and workers. No use in products with potential for ingestion. Lysmeral/Lilial is a known sensitizer and labeled as R43. Since many years an IFRA Standard exists which restricts the use of this material in consumer products. The allowed maximum values are by far much lower than the no effect levels derived from the animal studies.				

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2013	United Kingdom	Innospec Widnes Limited	Company-Manufacturer	8
Comment received				
We fully support the classification proposal of Reproductive Toxicity, Cat 2. We have been involved in the studies over the past five years. Our reasons for support are given in Reproductive Toxicty section				

Date	Country	Organisation	Type of Organisation	Comment number
09.12.2013	Germany		MemberState	9
Comment received				
In the summary of physico-chemical properties (Table 9) references with a validity of 4 have been used for "flash point" (118 °C, BASF_SDS (2006) Validity 4(not assignable))and "self-ignition-temperature" (250 °C, BASF_SDS (2006) Validity 4 (not assignable)). We recommend citation of measured values, available in the registration dossier or on the ECHA dissemination website.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.12.2013	United States	Takasago International Corporation	Company-Downstream user	10
Comment received				
This material is proposed for classification as a reproductive toxicant. We believe assignment to Category 2 is appropriate for the following reasons: 1) The materials is exclusively used in fragrances for cosmetic and household care products. As a result, dermal exposure is the most relevant route for consumers and workers. This material is not used in products with the potential for ingestion. 2) Availbale data provide support that the material would not be expected to cause any reproductive effects when exposure is by the dermal route. 3) The reproductive toxicity seen in male rats is of very limited relevance to humans because:				

a) Comparartive in vitro metabolism studies demonstrate that the toxic metabolite shown to be responsible for the observed reproductive effects is produced at significantly lower levels by humans compared to rats

b) The toxic effects show a clear threshold effect and claculated human exposure is well below this threshold

4) This substance is a recognized dermal sensitizer, already labeled R43. An IFRA Standard restricting the permitted use level of (and therefore exposure to) this material from consumer products has been in place for several years. The permitted maximum values are by far much lower than the no effect levels derived from the animal studies.

5) A dossier supporting the safe use of this substnace in cosmetic and pesonal care products has been submitted to the SCCS and is currently under evaluation. The calculated Margin of Safety is well above 100, which provides sufficient support for safe use of this substance.

In summary, the available data on reproductive toxicity is deemed more than sufficient for hazard assessment and scientifically appropriate to classify this substance as CMR2.

Date	Country	Organisation	Type of Organisation	Comment number
09.12.2013	Netherlands		MemberState	11
Comment received				
The Netherlands has several questions for clarification with regards to the proposed Repro. Cat. 2. for lysmeral made by the BASF SE in Germany. Species differences in response to lysmeral-induced testicular toxicity have been observed due to quantitative differences in metabolism and generation of TBBA, the metabolite believed to be responsible for the testis toxicity and spermatotoxic effects (p. 52). Is there any evidence that this mechanism is qualitatively not relevant to humans? Further, the evidence of the absence of effects on the testes in mice, guinea pigs, rhesus monkeys and rabbits is based on tests with limited duration, dose level and possibly limited general toxicity (not always stated). Please provide information on the general toxicity in these studies and whether these studies were performed at the maximum tolerable dose level. After acute and repeated oral and dermal administration of lysmeral to experimental animals and humans there is clear evidence of systemic absorption (p.16). Given the differences in load (mg/cm2), occlusion conditions, exposure period and possibly concentration between the absorption studies in rats and humans, can a conclusion on the difference between rats and humans be made? With respect to effects on development it is stated that the developmental effects are considered secondary to the materrnal toxicity. Please provide a justification for this. Please include a calculation of the ED10 showing whether a SCL is required or not.				

Date	Country	Organisation	Type of Organisation	Comment number
13.12.2013	United Kingdom	International Flavors and Fragrances	Company-Downstream user	12
Comment received				

This material is exclusively used in fragrances for cosmetic and household care products where skin exposure is the most relevant route of exposure to both consumers and workers. This material is not used in products with potential for ingestion.

Studies on this material indicate that no reproductive effects would be seen via the dermal route.

The reproductive studies seen in male rats in this study are of little relevance to humans because:
- the putative repro-toxic metabolite would be seen at significantly lower levels in humans
- The effects seen in male rats show a clear threshold effect and human exposure is far below this threshold

This material is classified as R43 (H317 according to CLP)and as such an International Fragrance Association (IFRA) Standard exists which restricts the use of this material in consumer products. The allowed maximum values for consumer exposure resulting from these IFRA standards are much lower than the no effect levels derived from the animal studies.

An SCCS dossier for safe use approval in cosmetics has been submitted and is currently under evaluation. The Margin of Safety is well above 100, which provides sufficient evidence for the safe use of the material

Given that the reproductive effects are observed only in oral gavage studies in animals and have limited relevance to humans, the classification as a CMR may be questioned. At most, a classification of Reproductive toxicity, Category 2 is supportable.

Date	Country	Organisation	Type of Organisation	Comment number
13.12.2013	Sweden		MemberState	13

Comment received

The Swedish CA do not support the proposed classification of 2-(4-tert-butylbenzyl)propionaldehyde (Cas no 80-54-6, hereafter named lysmeral) as a Category 2 reproductive toxicant (H361f). Instead we propose that lysmeral should be classified in repro 1B (H360F) based on the clear sign of testicular toxicity in dogs (LOAEL = 200 mg/kg, 14 days repeated dosing via gelatine capsules, but not clear if dose interval between 50 and 200 was examined) and rats (LOAEL = 50 mg/kg, independent of duration of treatment) and the adverse effects on fertility as indicated by the recording of a very low fertility index in a one-generation range-finding study at dose levels from 1700 ppm (~62 mg/kg).

The dossier submitter argues that there is mechanistic information that raises doubt about the relevance of the effects for humans and therefore a classification in Cat 2 is more appropriate. The arguments put forward by the dossier submitter (on page 55 of the CLH report) include but are not limited to the following:
a) "Species specificity for lysmeral induced testicular toxicity has been observed. Adverse effects of lysmeral on the male reproductive system at a clearly defined threshold dose have been found in rats whereas no evidence for testicular toxicity was observed in the mouse and guinea pig. Considering non-rodent species, the dog has been shown to be susceptible towards lysmeral induced testicular toxicity. In contrast, short-term oral exposure to rabbits did not indicate a potential of lysmeral to induce testicular toxicity. Furthermore in rhesus monkeys, no indication of testicular toxicity, at doses causing testicular toxicity in the rats, was observed."

The SE CA does not agree with this conclusion. Since there is evidence that it is the metabolite TBBA that is causing the toxicity a comparison of the plasma concentrations of lysmeral and the toxic metabolite across the species used would have been valuable in order to conclude regarding species specificity of lysmeral induced testicular toxicity. In addition, a closer examination of the data (see section 4.7.1.1) reveals that no signs of toxicity was observed at the highest dose tested in rabbits (300 mg/kg, 15 days gavage), in rhesus monkey (100 mg/kg, 5 days, via the feed) or in the guinea pig (5 days gavage 100mg/kg) so one can conclude that the potential of lysmeral to induce testicular toxicity in these species were not fully explored since to low dose levels were used.

b) To further support this argument the dossier submitter relates to the result from an in vitro comparative metabolism study.
"Species specificity for lysmeral induced testicular toxicity is reflected by species dependent differences in the conversion of lysmeral to TBBA in hepatocytes. TBBA formation in human hepatocytes is of low magnitude compared to rats and is comparable to levels found in the rabbit at toxicologically relevant doses, a species not sensitive to lysmeral induced testicular toxicity."

The SE CA do not agree with this conclusion. The complexity of an in vitro comparative metabolism study (where many phase I and phase II enzymes are involved) is such that one should not draw quantitative conclusions. Instead it should be used to draw qualitative conclusions - i.e. whether similar metabolites can be found in two different species. Overall, the experimental design as well as the data presentation of this study is poor and since there are no guidelines for this kind of studies it is very important that all study details are available otherwise the robustness of the study cannot be judged and thus it will be difficult to draw even qualitative conclusions. For example, basic information such as incubation time, viability of hepatocytes, source of human hepatocytes (pooled sample or not) and whether hepatocytes from animal species (as well as the one from humans) were used fresh or cryopreserved have not been included. In addition, there is no information on number of technical and biological replicates. The latter is especially of importance when evaluating the human data and the interindividual variability regarding metabolism. Furthermore, there is no information on what positive controls were used to make sure that the enzyme involved in the formation of TBBA and its glycine conjugate were functionally active. Finally, it would have been very valuable if hepatocytes from dogs (another species were testis toxicity was observed) had been included in the experiment.

In summary we do not think that the in vitro metabolism data should be used for conclusions regarding in vivo metabolic quantitative differences between species. The data presented are not robust and do not provide mechanistic information that raises doubt about the relevance of the effects for human. The data can be interpreted in many ways but it is interesting to note that the metabolite that is presumed to cause testis toxicity is formed in humans as well. Thus, the available data on reproductive toxicity is considered as clear evidence and therefore classification of lysmeral as a category 1B (H360F) reproductive toxicant is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
13.12.2013	France		MemberState	14
Comment received				
pg31 More detailed report of the study performed for five consecutive days in male mice or guinea pigs (Newberne 1990 B-C) would be welcome.				

pg33 The effects in the high dose treated group from the screening study in rabbits (BASF SE 2008C) are missing.

pg33 Thanks for reporting the ALL hepatic effects observed in the study on primates (Newberne 1990; Givaudan 1984G).

Table 14: thanks for specifying the number of replicate, which type of human hepatocytes have been used. If fresh, thanks for specifying the number of donors.

Anyhow, it seems dubious to override the overall in vivo metabolism database (such a huge in vivo database!!) with a single in vitro study.

The CLH report details the spermatotoxicity of Lysmeral through TBBA. However, there is no data showing that Lysmeral or other metabolites are not spermatotoxic per se. Moreover, the effects observed after dermal exposure (pg 34) tend to prove that Lysmeral could also be spermatotoxic per se (not (only) its metabolisms) as this route of exposure allows avoiding the first pass metabolism. FR believes that the data provided do not allow claiming that Lysmeral is spermatotoxic only through its TBBA metabolism and therefore recommend to classify it as reprotoxic category 1. It has to be noted that we have no idea how and when M7 metabolism (the most present with human hepatocyte) evolve.

Pg 28, it is stated that considering the repeated short and long term oral administration studies in rats, and as adverse testicular findings were observed already after a single oral administration, Lysmeral reprotoxic effects seems at least to be acute. They also are irreversible as described pg 29 "Leydig cells were described along with a decreased density of spermatozoa, nucleated cells and spermatoceles in the epididymides of the high dose animals. In the 4 week recovery group, the same testicular pathology was observed to a lesser extent."
To elaborate on this finale statement the raw data would be valuable.

As mouse and guinea pig exposed to TBT (but not TBB) show effects on testicules, metabolism pathways of these substances have to be provided (to see which other metabolites, they display). However, such statement as "No evident testicular toxicity observed » are not acceptable and details of the study should be provided if the read-across has to be taken into account.

Based on the available data on monkey showing spermatic effects on 50% of the individuals, together with the tremendous bunch of data on numerous animals displaying spermatotoxicity of similar substances in mouse and guinea pig as well, the fact that human metabolise this substance similarly to animals, the fact that these effects seem to appear quickly and in an irreversible manner, FR proposes to discuss a category 1A for fertility.

Pg40, the table 17, the post implementation loss indicate developmental effects on the top of fertility effects.
It is claimed that the developmental effects are due to maternal toxicity although this is only visible by a decrease in BWG at 6-8d. Thanks for providing the exact data together with the corrected BW (with uterus weight or by given BW after parturition). Indeed, it is written: "In high dose animals, reduced mean uterus weights (20% below controls) were observed."
Therefore, the effects observed on BW could be attributed to developmental effects of Lysmeral and FR proposes classification for development (1B) to be discussed as well.

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	Belgium	Procter & Gamble Corporation	Company-Downstream user	15

Comment received

☐ Adverse effects on fertility were observed in male rats – however, the extent of these effects was shown to be species specific. These effects are of little relevance to humans because in comparative in vitro metabolism studies, the toxic metabolite was seen at significantly lower levels in humans versus rats. Further, the toxic effects showed a clear threshold effect and expected human exposure is well below this threshold level.

☐ The toxicity effects were observed in rat studies via the oral route and this route of exposure for Lysmeral is not relevant for humans. The substance is exclusively used in fragrances in consumer products which come into contact with humans via the dermal route. Available information supports the view that reproductive effects would not be expected when the exposure is dermal.

☐ The substance is a known skin sensitizer and labeled as such (R43; H317). An IFRA Industry Standard exists already for many years which restricts the use of this substance in various consumer products – thus exposure is controlled. The allowed maximum use levels are by far much lower than the no effect levels derived from the animal studies.

☐ The substance is used exclusively in fragrances at low concentrations in cosmetic and household care products where dermal exposure is the most relevant route of exposure for both consumers and workers. The substance is not used in products intended for ingestion. Exposure via inhalation may occur but to a much lower extent.

☐ A comprehensive dossier has been submitted to the SCCS supporting the continued safe use of the substance in fragrances in cosmetics products – the dossier is currently under evaluation. The Margin of Safety was calculated and is well above 100, which provides additional supporting evidence for the safe use of the substance in these consumer products.

☐ In summary, a thorough review of all the available data related to reproductive toxicity is considered to be more than sufficient for a robust hazard assessment of this substance. Under current classification guidelines, it is considered appropriate to classify Lysmeral as CMR2 (Repro Cat 2, H361f: Suspected of damaging fertility).

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2013	United States	Firmenich SA	Company-Downstream user	16

Comment received

In addition to the toxicology data, further support is added to the proposed CMR2 classification as illustrated below:

Measures to limit exposure to this material have existed since 2003 via an IFRA standard based on skin sensitization. This standard was reviewed in 2007 utilizing the QRA methodology and again in 2008 setting limits in each respective category. These limits fall well below the no effect levels demonstrated in the animal studies that have been performed.

In addition, exposure to this material is solely through the dermal route as it is only used in fragrances for cosmetic and household care applications. Data supports that this route of exposure provides an insufficient dose to cause the reproductive effects of concern.

Finally, a dossier demonstrating a margin of safety greater than 100 has been submitted to the SCCS for safe use approval in cosmetics and is currently being reviewed.

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2013	France	CHARABOT	Company-Downstream user	17

Comment received

Available data support that no reproductive effects would be seen via the dermal route of exposure
The reproductive toxicity seen in male rats has low relevance to humans because
a) toxic metabolite is seen at significantly lower levels in humans than in rats
b) toxic effects show a clear threshold effect and human exposure is well below this threshold
In conclusion, available data package on reproductive toxicity is deemed more than sufficient for hazard assessment and scientifically appropriate to classify Lysmeral as CMR2.

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2013	France	ROBERTET S.A.	Company-Downstream user	18

Comment received

1)The available data support that no reproductive effects would be seen via the dermal route of exposure.
2)The reproductive toxicity seen in male rats has low relevance to humans because
a) toxic metabolite is seen at significantly lower levels in humans than in rats
b) toxic effects show a clear threshold effect and human exposure is well below this threshold

In conclusion, available data package on reproductive toxicity is deemed more than sufficient for hazard assessment and scientifically appropriate to classify Lysmeral as CMR2.

Date	Country	Organisation	Type of Organisation	Comment number
10.12.2013	United States	Research Institute for Fragrance Materials, Inc.		19

Comment received

[ECHA note: Comment provider has provided only an attachment (Attachment 1), part of the attachment was copied below]

After review of the studies and the background data available on the fragrance ingredient, BMHCA, it is the reviewers' opinion that BMHCA has a propensity towards producing adverse male reproductive effects in rats and dogs. These effects do not appear to be ubiquitous in all animals, and have not been demonstrated in all the reported studies in rats and dogs. It should be noted that the reproductive studies in rats and dogs has low relevance to human

health because the toxic metabolite is seen at significantly lower levels in humans than in rats and the toxic effects show a clear threshold effect and human exposure is well below this threshold. No testicular effects were observed in rhesus monkeys following administration at one dose level for five days.

The data support that no reproductive effects would be expected via the dermal route of exposure.

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2013	United Kingdom	Innospec Widnes Limited	Company-Manufacturer	20

Comment received

(1) The formation of reprotoxic metabolites is species specific, and has a much stronger impact on rats than humans

(2) The substance is used in applications where the mode of contact with humans will be dermal. The reporductive toxicity effects in the studies were all observed in studies via an oral route and therefore are very much an extreme worst case for human exposure and risk assessment

(3) The substance is used in very low concentrations in end products which means that human exposure will only ever be at very low doses. The levels seen to cause reproductive toxicity effects in these studies would never be reached in normal use. In addition, the product has a very low odour threshold, which reduces the possibility of accidental high exposure.

(4) The reprotoxic effects seen in such animal studies are not representative of the impact on humans.

We conclude, therefore, that the proposed classification of Reproductive Toxicity, Category 2 is scientifically supported.

Attachment received : 1

1. *Research Institute for Fragrance Materials, Inc (filename: BMHCA ECHA CLP Comments Final 2013 12 10.doc)*, submitted by Research Institute for Fragrance Materials, Inc. was partially copied in to the table. Refer to comment no. 19.