COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 26.09.2023

Substance name: *p*-cymene; 1-isopropyl-4-methylbenzene; 3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal [1]; 3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [2] ; 4-isopropylbenzaldehyde; cuminic aldehyde [3] ; 4-isopropylbenzoic acid; cuminic acid [4]
CAS number: 99-87-6; 103-95-7 [1]; 7775-00-0 [2]; 122-03-2 [3]; 536-66-3 [4]
EC number: 202-796-7; 203-161-7 [1]; 231-885-3 [2]; 204-516-9 [3]; 208-642-5 [4]
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2023	Germany		MemberState	1
Comment received				
The efforts of the DS to prepare a CLH proposal for several substances as a grouping approach are highly acknowledged. The CLH proposal provided for commenting includes a group of five structurally similar substances; four substances (p-cymene, 3-p-cumenyl-2-methylpropionaldehyde, 3-(p-cumenyl)propionaldehyde and 4-isopropylbenzaldehyde) that are - or are predicted to be - metabolised to 4-isopropylbenzoic acid (4-iPBA), and the metabolite 4-iPBA itself. The metabolite 4-iPBA itself is not registered under REACH, but reported to be a testicular toxicant. Based on that inherent toxic property, the dossier submitter (DS) proposes to address several substances that have been shown to form 4-iPBA either in vitro or in vivo together using a category approach. In principle, the category approach is supported, however, there are some elements with respect to the category approach that deserve further attention/clarification. 1) Selection of substances Were there more substances retrieved that might possibly form 4-iPBA that were excluded (e.g. based on longer/more complex side chains)? 2) Consideration of metabolism While it is evidenced by in vitro/in vivo data that 4 of the substances covered in the dossier form iPBA, there are 2 aspects that deserve further attention. For 2 substances (EC 231-885-3 and EC 203-161-7) conversion to 4-iPBA will lead to formation of further metabolites. The impact of these additional metabolites should be addressed. Further, there might be differences in the velocity of the formation of 4-iPBA. Therefore, for some of the category members, the simultaneous presence of intact molecule along with breakdown product is considered likely. These two aspects might have an impact on differences in potency between the substances (see also ECHAs RAAF document). 3) Consideration of absorption/systemic bioavailability Based on chemical structures and differences in some physicochemical properties (e.g.				

water solubility, logPow) there might be differences in uptake/systemic absorption via the relevant uptake route(s) which could have an influence on the potency.
However, as these elements do not question the formation of the final metabolite 4-iPBA considered as ultimate toxicant for testicular toxicity the category approach is supported.

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France	Laboratoire Puressentiel	Company-Manufacturer	2

Comment received

Puressentiel is a memeber of EFEO. EFEO supports the opinion of IFRA fully.
Essential oils are obtained from natural raw material of plant origin. The originating plants are used as food or traditionally in cosmetics or in traditional medicine, often as active pharmaceutical ingredient. Such is the case for orange, lemon, peppermint, origano and thyme oil (food) or for neroli, rose and lavender oil (cosmetic) or eucalyptus, fir needle, lavender and also turpentine oil (active pharmaceutical ingredient in traditional medicine). Essential oils and / or the related plant material have been used for many centuries, if not millenia. The plants containing the essential oils have been part of every day life for even longer.
Essential oils also play a vital part as starting material for bio-based organic chemicals. They are an important source for renewable carbon. They are thus an integral part of Europe‘s net-zero strategy.
Essential oils are substances (1): therefore, they are classified according to test data if robust test data is present. If no data are available they are classified in a read-across process as if they are intentional mixtures. This classification is a well balanced base for a safe use of essential oils and other naturally occuring substances.
Most plants use either one of two pathways to produce the constituents of essential oils: Terpenic compounds are based on an isoprene-unit (=C5H8) and are produced by the mevalonate pathway. Phenolic compounds are produced by the shikimate pathway. A number of substances like para-cymene are therefore ubiquitous in essential oils.
The VCF database (https://www.vcf-online.nl/VcfHome.cfm) on published volatile compounds in natural (processed) food products lists 39 food sources in which over 3000 ppm (0.3%) of p-cymene had been analytically found including common foods such as citrus fruits, mint oils, origanum, rosemary, thyme, pepper, celery or cardamon among many others. Similarly, essential oils used for naturals-based consumer products widely contain p-cymene. Thus the International Fragrance Association (IFRA) maintains a labelling manual on natural complex substances (NCS) very commonly used in the industry containing 278 entries. 127 of those contain p-cymene, and the content is above 0.3% in 87 (31%) NCS like essential oils.
Table 1 (joint document) lists the essential oils with the most relevant exposure to consumers in the EU. The production and exposure data has been cumulated from company sources since so far no data are publically available. The para-cymene content is based on data from IFRA.
In food and cosmetics essential oils are only used in low concentrations: their content in the final food mimicks the use of spice or herb. Thus the exposure to consumers of para-cymene by food containing essential oils is similar tob y food containing spices and herbs. In cosmetics and fragrances essential oils are added to provide a sensory impact similar to smells humankind has been used to over the centuries: the final concentration of the essential oils are mostly far below 0.2%. In traditional medicine, the concentration of essential oils is higher. However, the exposure is only for a limited time. For most essential oils used as active pharmaceutical ingredients their use is regulated by monographs of the HMPC. Risk and hazard ofthe applications were evaluated during the establishment oft he

monograph.
A safe history of consumption and use of essential oils containing para-cymene has thus been established. In addition it was shwon that the bio-pathway leading to adverse effects in rats is not relevant to humans (ssee opinion of IFRA).
A classification of para-cymene as CMR category 1B based solely on male rats would potentially lead to a number of essential oils classified as CMR category 1B as well. These essential oils could in effect no longer be used in cosmetics and consumer goods, thus stopping the use and therefore the production of essential oils in Europe.
Considering that the effects have only been observed on male rats, such a classification is not warranted. The classification of CMR category 2 – it para-cymene needs to be classified at all – has to be considered.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Opinion_para_Cymene.docx

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France	COSMED	Industry or trade association	3

Comment received

Le Consortium HE remercie l'Agence européenne des produits chimiques de lui donner l'occasion de commenter le dossier proposant une classification et un étiquetage harmonisés pour le p-cymène. Le CONSORTIUM HE n'est pas en accord avec la classification Reprotoxique 1B du p-cymène proposée par le dossier CLH. Nos commentaires sont développés dans ce document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONSORTIUM HE- vd commentaires CLH REPORT P-CYMENE.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Germany	EFEO European Federation of Essential Oils	Industry or trade association	4

Comment received

EFEO represents about 200 companies in the production, import, trade and use of Essential Oils and other smelling or tasting plant extracts – collectively referred to as Natural Complex Substances (NCS).

EFEO fully supports the mechanistic analysis of species relevance provided by Givaudan.

Essential Oils are natural complex substances (NCS). They are obtained from natural raw materials of plant origin. The originating plants are used as food or traditionally in cosmetics or in traditional medicine, often as active pharmaceutical ingredients. Such is the case for orange, lemon, peppermint, oregano and thyme oil (food) or for neroli, rose and lavender oil (cosmetic) or eucalyptus, fir needle, lavender and also turpentine oil (active pharmaceutical ingredient in traditional medicine). Essential Oils and / or the related plant material have been used for many centuries, if not millennia. The plants containing the Essential Oils have been part of everyday life for even longer.

Some Essential Oils – such as turpentine oil – also play a vital part as starting material for bio-based organic chemicals. They are an important source for renewable carbon. They are thus an integral part of Europe‘s net-zero strategy.

Essential Oils are substances (1): therefore, they are classified according to test data if robust test data is available. If no data is available, they are classified according to the classification of their constituents using the (intentional) mixture approach. This classification procedure follows the UN GHS rules.

Most plants use either one of two pathways to produce the constituents of Essential Oils: Terpenic compounds are based on an isoprene-unit (= C5H8) and are produced by the mevalonate pathway. The mevalonate pathway is the dominant source for Essential Oils, and in terms of volume, essential oily mainly comprising monocyclic terpenes are clearly dominating the market (e.g. mint oils, eucalyptus, turpentine oil). P-cymene is an aromatic hydrocarbon belonging to the cyclic monoterpenes, and it is contained in the majority of oils comprising monocyclic terpenes. It is ubiquitous in Essential Oils.

(1) Essential Oils are classified as UVCBs under REACH (Substances of unknown or variable compositions, complex reaction products or of biological origin), mostly because of their variable composition. Due to the complex nature of identification, a guidance document was created in order to align the REACH registration process (https://echa.europa.eu/view-article/-/journal_content/title/guidance-on-substance-identification-for-essential-oils-now-available).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFEO - comments to clh p-cymene.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Germany	Symrise AG	Company-Manufacturer	5
Comment received				
I on behalf of Symrise AG would like to highlight our comments and our comprehensive counter-argumentation is outlined in the attached PDF document called "Symrise Response on CLH Proposal for Group para-Cymene 2023-09-22" ECHA note – An attachment was submitted with the comment above. Refer to public attachment Symrise Response on CLH Proposal for Group para-Cymene 2023-09-22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Switzerland	Givaudan	Company-Manufacturer	6
Comment received				
Please find the comments in the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22 - public.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	France		MemberState	7

Comment received
Toxicokinetics: Although we can agree on structural similarities between the substances, a common mode of action passing by the formation of a common metabolite (4-iPBA) is not so clear. From table 6, 4-iPBA was not detected as a metabolite in some in vitro studies in humans. Moreover, when formation of 4-iPBA was identified, it does not seem quantitatively significant. Could you please discuss further these points?

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2023	Germany		MemberState	8
Comment received				
1) Adverse effects on sexual function and fertility With respect to species differences, formation of 4-iBPA was only indirectly identified by the presence of low amounts of 4-iPBA-CoA in human hepatocytes while 4-iBPA was below detectable levels in the reported studies when assessed in human hepatocytes. This might either point to differences in sensitivity between species or indicate that metabolism occurs at an extrahepatic site (e.g. directly in the target tissue). However, an in vivo study performed with EC 203-161-7 in male rats pointed to much lower levels 4-iPBA-CoA in testes when compared to liver. Therefore, formation of the ultimate metabolite in humans could be an issue for debate on human relevance. But – as indicated by the DS, adverse effects on testis and sperm were not only reported for the rat, but in a second species, i.e., rabbits (for which 4-iPBA formation was lower when compared to rats), so there are good arguments against a mechanistic explanation published by industry suggesting rat specifity of the mode of action with respect to testicular- and spermatotoxicity. Qualitative differences in toxicities between the substances, effects in females and developmental effects might also be the consequence of other/additional pathways (e.g. independent from 4-iPBA formation). 2) Developmental toxicity: For developmental toxicity, the available data/the reported effects show a less consistent picture between the substances which might be due to the heterogeneity of the available study types. Qualitative differences in developmental effects might also be the consequence of other/additional pathways (e.g. independent from 4-iPBA formation). Therefore, it might be sufficient to base the classification for that particular endpoint on weight of evidence only rather than read across.				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	United Kingdom	IFRA UK	Industry or trade association	9
Comment received				
IFRA UK does not support the reproductive toxicity classification that has been proposed. ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA UK CLP Consultation Response p-cymene; 1-isopropyl-4-methylbenzene (202-796-7) – September 2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France	Laboratoire Puressentiel	Company-Manufacturer	10

Comment received

the ECHA Guidance on the Application of the CLP Criteria (ECHA, 2017) needs to be considered when evaluating justification for a CMR 1B classification. The document states that “Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should be taken into account in the classification and should not be used again as a modifying factor for potency.” and “In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries to a lower potency group.” (3.7.2.6.5. Modifying factors).

There is convincing published and peer reviewed evidence that Cyclamen Aldehyde, p-cymene and other compounds lead to the formation of 4-iPBA in rats and induce 4-iPBA-CoA accumulation in the testes and livers, with a marked species difference and of low or absent relevance to humans. Thus, a C&L of Repro 1b is not justified.

P-cymene is a central component of many naturals used for flavouring foods and as traditional medicine. Recently, the Flavor and Extract Manufacturers Association (FEMA) Expert Panel affirmed the generally recognized as safe (GRAS) status (Cohen et al, 2021) of Origanum Oil (FEMA 2828), Savory Summer Oil (FEMA 3013), Savory Summer Oleoresin (FEMA 3014), Savory Winter Oil (FEMA 3016), Savory Winter Oleoresin (FEMA 3017), Thyme Oil (FEMA 3064) and Thyme White Oil (FEMA 3065), with no evidence of concern for reproductive or developmental toxicity (WHO, 2006). P-cymene was identified in all these naturals and ranged from 5 to 44%.

The VCF database (https://www.vcf-online.nl/VcfHome.cfm) on published volatile compounds in natural (processed) food products lists 39 food sources in which over 3000 ppm (0.3%) of p-cymene had been analytically found including common foods such as citrus fruits, mint oils, origanum, rosemary, thyme, pepper, celery or cardamon among many others (See ANNEX I). Similarly, essential oils used for naturals-based consumer products widely contain p-cymene. Thus the International Fragrance Association (IFRA) maintains a labelling manual on natural complex substances (NCS) very commonly used in the industry containing 278 entries. 127 of those contain p-cymene (See ANNEX II), and the content is >0.3% in 87 (31%) NCS like essential oils. These include widely different products such as tea tree oil, mandarin oil, lemon essence, cinnamon oil or pine oil. Additionally, considering those NCS only used by one or few companies, this number is even clearly higher.

The European Food Safety Authority (EFSA) estimated daily intake of p-cymene as 926μµg/d/capita (EFSA, 2015)(quantitative metabolism would lead to 1133μ□g/d/capita of 4-iPBA). However, this is only based on flavours intentionally added to foods and it does not take into account the amounts naturally present in foods and the amounts coming from consumer products. Given the common occurrence of p-cymene in multiple foods and also in natural consumer products, the actual cumulative exposure is unknown.

Based on all these considerations, including history of safe food consumption in humans, the established toxicity mechanism is of questionable relevance in humans and therefore the ECHA Guidance (ECHA, 2017) on the Application of the CLP Criteria should apply:

- “Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should be taken into account in the classification.
- In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries to a lower potency group.”

Thus a CMR 1B for male reprotoxicity is not warranted and a CMR 2 classification based on the clear effects in rats only, for which a rat specific mechanism was shown, is more appropriate.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Opinion_para_Cymene.docx

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	France	COSMED	Industry or trade association	11

Comment received

I. Différences de mécanisme entre espèces :

Il est indiqué dans le rapport CLH que « In the present dossier, adverse effects on testis and sperm are indicated in a second species, i.e., rabbits (details are given in section 10.10), thus contradicting the rat specific mechanism of toxicity proposed by Natsch and co-workers (2021)».

En ce qui concerne le p-cymène, les études de reprotoxicité ont été réalisées uniquement chez le rat. Aucune étude n'a été réalisé sur d'autre espèces. Pour rappel, l'étude de Natsch (Natsch et al., 2021) a démontré que les effets néfastes sur la reproduction chez le rat sont dus à la métabolisation du p-cymène en acide p-isopropylbenzoique (iPBA). Ce dernier va ensuite être converti en p-isopropyl benzoyl Coenzyme A. Ce p-isopropyl benzoyl CoA s'accumule dans les hépatocytes de rat à des niveaux stables, cela est corrélé avec la toxicité sur la reproduction chez les rats. En revanche l'ester de CoA est éliminé au fil du temps dans les hépatocytes humains. Ces connaissances mécanistiques spécifiques à l'espèce soulèvent des doutes importants quant à leur pertinence chez l'homme.

Selon la section 3.7.2.1.1 de l'annexe I du CLP, « lorsqu'il existe des informations mécanistes qui soulèvent des doutes quant à la pertinence de l'effet pour l'homme », une catégorie 1 n'est pas justifiée. De plus, le guide de l'ECHA sur l'application des critères CLP (ECHA, 2017) doit être pris en compte lors de l'évaluation d'une classification Repro 1B. Ce dernier indique que "Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should have been taken into account in the classification and should not be used again as a modifying factor for potency» et "In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries to a lower potency group."

II. Utilisation humaine du p-cymene :

Le p-Cymène, un composant présent dans de nombreuses substances naturelles, est utilisé en alimentaire et en médecine traditionnelle. Selon la FDA (Food and Drug Administration), le p-cymène est considéré comme « généralement reconnu comme sûr » (GRAS) lorsqu'il est utilisé en tant qu'agent aromatique (FDA, 2006).

De plus, le groupe d'experts de la Flavor and Extract Manufacturers Association (FEMA) a confirmé le statut « généralement reconnu comme sûr » (GRAS) de l'huile d'origan (FEMA 2828), de l'huile de thym (FEMA 3064) et de l'huile blanche de thym (FEMA 3065).

III. Impacts de la classification du p-cymene en Repr. 1B :

Une classification du p-cymène comme reprotoxique de catégorie 1B basée uniquement sur des études chez le rat, conduirait potentiellement à la classification d'un certain nombre

d'huiles essentielles comme reprotoxique de catégorie 1B également. Ces huiles essentielles pourraient en effet ne plus être utilisées dans les cosmétiques, ce qui impacterait fortement l'utilisation et donc à la production d'huiles essentielles en Europe.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CONSORTIUM HE- vd commentaires CLH REPORT P-CYMENE.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Germany	EFEO European Federation of Essential Oils	Industry or trade association	12

Comment received

In food and cosmetics Essential Oils are only used in low concentrations: their content in the final food mimics the use of spice or herb. Thus, the exposure to consumers of p-cymene by food containing Essential Oils is similar to food containing spices and herbs. In cosmetics and fragrances Essential Oils are added to provide a sensory impact similar to smells humankind has been used to over the centuries. In traditional medicine, the concentration of Essential Oils is higher – however, the exposure is only for a limited time. For most Essential Oils used as active pharmaceutical ingredients their use is regulated by monographs of the HMPC (Committee on Herbal Medicinal Products at EMA). Risk and hazard of the applications were evaluated during the establishment of the monograph.

The VCF database (https://www.vcf-online.nl/VcfHome.cfm) on published volatile compounds in natural (processed) food products lists 39 food sources in which over 3.000 ppm (0,3 %) of p-cymene had been analytically found including common foods such as citrus fruits, mint oils, oreganum, rosemary, thyme, pepper, celery or cardamom among many others. Similarly, Essential Oils used for naturals-based consumer products widely contain p-cymene. Thus, data from industry shows that about 1/3 of all natural products used in flavors and fragrances contain more than 0,3 % p-cymene. These Essential Oils would be classified as Repr. 1B if p-cymene is classified as Repr. 1B.

Indeed, based on industry figures of the p-cymene content in Essential Oils, the world production and the use of the Essential Oils in the EU, the consumption of p-cymene across all applications by Essential Oils is roughly 1.100 µg/capita/day. No negative effects of this consumption have been reported.

A safe history of consumption and use of Essential Oils containing p-cymene has thus been established. In addition, it was shown that the bio-pathway leading to adverse effects in rats is not relevant to humans (2), (3), (4).

A classification of p-cymene as Repr. 1B based solely on male rats would potentially lead to a number of Essential Oils classified as Repr. 1B as well. These Essential Oils could in effect no longer be used in cosmetics and consumer goods, thus stopping the use and therefore the production of Essential Oils in Europe and worldwide.

Considering that the effects have only been observed on male rats, such a classification is not justified.

(2) Laue, H., et al., p-Alkyl-benzoyl-CoA conjugates as relevant metabolites of aromatic aldehydes with rat testicular toxicity - studies leading to the design of a safer new fragrance chemical. Tox. Sci., 2017. 160(2): p. 244-255.

(3) Natsch, A., et al., A species specific metabolism leading to male rat reprotoxicity of Cyclamen aldehyde: in vivo and in vitro evaluation. Food Chem Toxicol, 2021. 153: p. 112243.

(4) Laue, H., et al., Benzoyl-CoA conjugate accumulation as an initiating event for male reprotoxic effects in the rat? Structure-activity analysis, species specificity, and in vivo relevance. Arch. Toxicol., 2020. 94(12): p. 4115-4129.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFEO - comments to clh p-cymene.pdf

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Germany	Symrise AG	Company-Manufacturer	13
Comment received				
Repr. 1B H360FD (see pages 2 -6 of our attachment) ECHA note – An attachment was submitted with the comment above. Refer to public attachment Symrise Response on CLH Proposal for Group para-Cymene 2023-09-22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2023	Switzerland	Givaudan	Company-Manufacturer	14
Comment received				
Please find the comments in the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22 - public.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	France		MemberState	15
Comment received				
Fertility: Clear effects on both male and female fertility were reported for p-cymene in the OECD 422 study, including in particular alteration of testis and sperm, irregular cycles and reduction of fertility index. Similar effects were observed with 3-p-cumenyl-2-methylpropionaldehyde in an OECD 415 study. Sperm alterations leading to a drastic decreased fertility were reported in males when mated with untreated females. Treated females mated with untreated males also present adverse effects, such as decreased implantation sites and mortality of pups.				

Sperm alterations were also found for this substance in a 28-day and a 90-day study in rats. Effects on sperm were suggested in a 14-day study in rabbits.

No reproductive toxicity study is available for other substances. Instead, repeated toxicity studies exist for 3-(p-cumenyl)propionaldehyde and 4-iPBA. Sperm and testicular alterations were consistently found.

No toxicological study is available for 4-isopropylbenzaldehyde.

TBBA and lysmeral are cited as structurally similar substances without further details. It would have been useful to provide the scientific rationale behind in the CLH report.

Overall, there is clear evidence of reproductive effects justifying a classification as Repr. 1B for fertility for 3 of the 4 substances considered. We note that there is no toxicological study with 4-isopropylbenzaldehyde. In the absence of toxicokinetics data, the read-across is only based on QSAR and structural and physico-chemical similarity.

Development:

Decreased body weight and mortality (pre and post-natal) were found in pups in the OECD 422 with p-cymene. No teratogenicity study is available for this substance.

For 3-p-cumenyl-2-methylpropionaldehyde, only a reduction of body weight is found in the OECD 414 study in rats. In contrast, in the OECD 415 study, an increase of pup mortality was described. Pups also presented lenticular opacity and decreased body weight.

There is no developmental toxicity data for other substances.

Overall, there is clear evidence of developmental toxicity, characterised by an increase of pup mortality, based on studies performed with p-cymene and 3-p-cumenyl-2-methylpropionaldehyde. This justifies a classification as Repr. 1B for development. Concerning extrapolation of this classification to other considered substances, it would be useful to have a deeper read-across rationale – for example according to RAAF guidance document.

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2023	United Kingdom	Health and Safety Executive	National Authority	16

Comment received

‘The DS has proposed classification with Repr. 1B (H360D) for developmental toxicity for all substances in the group. We note that read-across has been conducted on the basis that the substances share a common metabolite, 4-iPBA. However, in the absence of developmental toxicity data on 4-iPBA, or a proposed mode of action for 4-iPBA-induced developmental effects, we would welcome clarification from the DS on their justification for using read-across to assess adverse effects on development for all substances in the group.

In addition, we note that, in the OECD TG 415 study with 3-p-cumenyl-2-methylpropionaldehyde (Study report, 2011a), lenticular opacities were observed from PND 16 at a dose level of 150 mg/kg bw/d. Is it possible that the lenticular opacities occurred as a result of exposure via lactation or during weaning to adult diet?’

PUBLIC ATTACHMENTS
1. IFRA UK CLP Consultation Response p-cymene; 1-isopropyl-4-methylbenzene (202-796-7) – September 2023.pdf [Please refer to comment No. 9]
2. CONSORTIUM HE- vd commentaires CLH REPORT P-CYMENE.pdf [Please refer to comment No. 3, 11]
3. EFEO - comments to clh p-cymene.pdf [Please refer to comment No. 4, 12]
4. Symrise Response on CLH Proposal for Group para-Cymene 2023-09-22.pdf [Please refer to comment No. 5, 13]
5. Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22 - public.pdf [Please refer to comment No. 6, 14]

CONFIDENTIAL ATTACHMENTS
1. Opinion_para_Cymene.docx [Please refer to comment No. 2, 10]
2. Givaudan Response to CLH report Proposal for Harmonized Classification Cyclamen and Group - Sept.22.pdf [Please refer to comment No. 6, 14]