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SYMRISE RESPONSE TO THE CLH REPORT "PROPOSAL FOR HARMONIZED CLASSIFICATION AND LABELLING OF THE GROUP OF PARA-CYMENE, 3-PARA-CUMENYL-2-METHYLPROPIONALDEHYDE, 3-(PARA-CUMENYL)PROPIONALDEHYDE AND 4-ISOPROPYLBENZALDEHYDE BASED ON THE COMMON METABOLITE ISOPROPYLBENZOIC ACID (4-IPBA OR CUMIC ACID)

To Whom It May Concern,

Please find attached the response from Symrise to the CLH report "Proposal for Harmonized Classification and Labelling of the group of para-cymene, 3-para-cumenyl-2-methylpropionaldehyde, 3-(para-cumenyl)propionaldehyde and 4-isopropylbenzaldehyde based on the common metabolite ISOPROPYLBENZOIC ACID (4-iPBA or Cumic Acid)

Yours sincerely,

Symrise AG

[redacted]

Introduction
KEMI provided a CLH proposal for a group of substances to be classified with Repr. 1B H360FD based on the formation of a common “critical” metabolite.
The following detailed assessment focuses mainly on one member of the group, para-cymene and does not intend to repeat the arguments/rationale provided by Givaudan. It will however cross-reference to that document to some extent.

Summary
We do not agree that data at hand justify a classification of para-cymene as Repr. 1B (H360FD) neither based on the scientific arguments provided nor according to the provisions of the CLP directive based on the following rationale:

- Effects were noted **only in rats** in a reproductive screening study (OECD 422)

- Rats compared to other species including humans. show for para-cymene a very different metabolism (**qualitatively and quantitatively**) especially with regard to the formation of the critical metabolite 4-iPBA potentially responsible for the effects noted in the rat

- As the metabolic formation of 4-iPBA according to the proposal is considered the key event for the read across and for assessing the substances as a group it is important to have quantitative data for the different species to allow a comparison and to assess the relevance for humans. The statement that a common metabolite is formed without quantitative data at hand does not allow a conclusion to which extent effects in rats are relevant for humans at all. This is clearly stated in the CLP Regulation 3.7.2.3.2 and 3.7.2.5.5 addressing the relevance of toxicokinetic differences. The data at hand clearly support pronounced toxicokinetic differences between rats and humans.

- For rats, in addition, a species-specific MOA based on 4-iPBA is very likely. Thus, further questioning the relevance of findings in this species for humans even if small amounts are formed in humans. A very effective glucuronidation of 4-iPBA (cuminic acid) in humans makes accumulation of this molecule unplausible (8).

- Para-cymene is part of the normal human diet (flavoring foods/herbs, and traditional medicine) with background values of around 1 mg/person/day or slightly higher. Thus, humans are exposed to this chemical since millennia. However, no indications were found that groups with higher exposure might have a higher risk of reproductive toxicity (e.g. evident by lower sperm quality). This is in line with observations in marsupials.

- Studies in marsupials demonstrate a pronounced difference in the para-cymene metabolism between species eating either a diet high or low in para-cymene content, with well-adapted species showing a more efficient oxidation of the compound. This might also explain the different metabolism in laboratory rats being exposed to this chemical the first time with the beginning of the respective study. In addition, for the group with the high content of para-cymene in the diet, no indication for a disturbed reproduction was reported.

- Modifying factors (intake of different fats) on the formation of 4-iPBA were noted in humans, indicating an even more complex and variable metabolic profile in humans.

Considering (1) the limited experimental data for para-cymene, which was only tested in rats, (2) the profound quantitative and qualitative differences in metabolism between rats and other species including humans, (3) a rat specific MOA, and (4) the lack of any reports of reproductive effects in other species with a high natural exposure to para-cymene (e.g. certain marsupials) or humans although being exposed to para-cymene for millennia, only a classification as Repr 2 (H361) is in line with the provisions of the CLP Regulation.*

1. Read across among the group members

The read across and grouping to conclude the same classification and labelling for the different members of the group is based on the formation of the common "critical" metabolite 4-iPBA.
This approach, however, does not take into account the chemical differences of the members of the group resulting in different toxicokinetics and reactivity in a biological system.
Important to note here are the differences of para-cymene compared to the aldehydes and 4-iPBA with regard to

- Water solubility
- Partition coefficient octanol/water

and the differences in chemistry

- Reactivity towards proteins (aldehydes)

These differences alone will have a direct effect on toxicokinetics (even without considering the metabolism) of the different members of the group and might be the reason why in the ARN (1) para-cymene had not been put into the same group as the other substances discussed here.

* Footnote: Furthermore the proposed classification entry does not conform with Section 1.6.3.3.3 of the ECHA Guidance on CLP for 'Additivity vs non-additivity of hazards' for mixtures as the need for classification of mixtures based on the sum of the concentrations of individual substances forming the same metabolite has not been scientifically justified in this case and is not normally applicable to reproductive hazards under ECHA Guidance on CLP (*Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, 2017)*

2. Quantitative and qualitative difference in the metabolism of para-cymene in rats compared to other species

As mentioned above, already the main grouping argument, namely the read across of the findings among the group and the proposal for Repro 1B H360FD, is the formation of the common metabolite 4-iPBA.

The formation of a relevant amount of this metabolite is not questioned for the rat. Thus, at least for the rat this hypothesis is supported by respective kinetic data.
Focusing on the oxidation on the methyl group and the formation of 4-iPBA as the key step for the reproductive toxicity of para-cymene is, however, at least for humans not correct as ring oxidation and oxidation of the propyl side chain seem to be the predominant metabolic pathway in contrast to the rat (5). Similar findings were noted for guinea pigs (2) (see CLH report page 10) or in rabbits (3, 4) and especially in humans (5). For example, in guinea pigs only trace of amounts of iPBA were found (2). This is also reported in the CLH dossier but not further discussed.

In summary, neither for guinea-pigs, rabbits or humans 4-iPBA was identified as a quantitative relevant metabolite and other oxidation pathways seem to be more important than in rats.
In a study with marsupials (7) the influence of a diet rich or poor in para-cymene on the metabolic profile was investigated. The diet being rich in para-cymene resulted in a significant difference in the metabolic profile in the respective species, with a much higher rate of more extensively oxidised metabolites (containing 3 or 4 oxygen atoms). Interestingly, no 4-iPBA was found in these species in contrast to rats investigated in parallel and with the same treatment scheme, in which this metabolite was very prominent. Additionally, it was shown that the glucuronidation of 4-iPBA (cuminic acid) is extremely effective in humans compared to Nonsteroidal anti-inflammatory drugs (NSAID). Taken this into account an accumulation of 4-iPBA in humans is unplausible (8).
These findings further support that humans are likely to show a different metabolism e.g. compared to rats, due to continuous naturally occurring exposure to para-cymene since millennia.
The differences in the metabolism and its relevance for the assessment was also highlighted in the ‘Safety Assessment of Certain Food Additives’ by JECFA in 2006 (6).
These pronounced qualitative and quantitative difference in the metabolism, however, need to be evaluated from a toxicological point of view to assess the relevance of findings in the rat for humans but also from a regulatory point of view to derive a classification according to the provision of the CLP directive 3.7.2.3.2 and 3.7.2.5.5. The pronounced quantitative differences in toxicokinetic of para-cymene were neither discussed nor assessed with regard to the respective CLP provision in the current CLH proposal.

3. Rat specific mode of action (MOA)

Instead of repeating here the data and arguments supporting a rat-specific mode of action which can explain the findings noted in respective in vivo studies we refer to the comments document submitted by Givaudan.
In this document also new data are presented to support this rat-specific MOA and the clear differences between rats and humans.

For para-cymene, “critical” effects were reported only in a screening study [redacted] in the rat for which the formation of the postulated critical metabolite is quantitatively quite different and a rather species-specific kinetics and MOA is reported.

No effects in other species showing a metabolism which is closer to the one reported in humans are reported.

Any decision based on the current data set needs to be done carefully due to this data gap. Based on the CLP criteria, the data at hand and the argumentation provided above a classification as Repr. 2 H361F (some evidence) could be derived but certainly not for Repr. 1B H360 FD (clear evidence) for the assessment in humans. Alternatively, the decision could be postponed and a substance evaluation initiated, in which further studies could be requested to elucidate/clarify the relevance of the rat findings for humans.

Thus, besides the pronounced quantitative differences between rat and humans in the formation of the “critical” metabolite, there is also quite some evidence that the effects noted in rats are species-specific and can be explained by a rat-specific MOA.
This clearly shows that effects noted in rats cannot be taken 1:1 to assess the potential in humans.

4. Background exposure of humans via the normal diet

Humans have been exposed to the natural ingredient para-cymene in the diet (flavouring foods/herbs and traditional medicine, (9)) for millennia already without showing a higher prevalence of sperm effects/reproductive toxicity in regions with a higher intake of this compound compared to regions with a lower intake. A background exposure of >1 mg day from the diet can be expected, for example, for Europe (6) (for further details please see the document from Givaudan). This different metabolic profile noted in humans might be explained by the continuous exposure and induction of different Cytochrome P450 isoenzymes resulting in much more and faster oxidation of the isopropyl side chain or the benzyl ring compared to the methyl group. As discussed above already, a different metabolism has also been observed in generalist and specialist folivorous marsupials (7). These findings support that a continuous exposure to para-cymene has a significant effect on the metabolic profile. This might be an additional factor explaining the metabolic differences seen between humans and naive laboratory animals being exposed to it the first time in a study.

Recent studies (10, 11) in humans show an even more complex pattern, as diets based on different fats (11) have shown an effect on the formation of 4-iBPA. Unfortunately, the respective studies provided only relative changes for this metabolite but no quantitative data to allow a quantitative comparison with rats.

5. In vivo findings

The findings noted in in-vivo studies are described and discussed in detail in the response by Givaudan and we will not repeat those here.
We would however like to draw the attention to the following facts relevant for para-cymene

- Moreover, the proposal to also classify the substances as developmental toxic 1B (H360D) is difficult to understand. At least for para-cymene only findings in an [redacted] are available. As discussed already above to use the (qualitative) formation of 4-iPBA as a sole basis for a read across to other group members and to different endpoints beside male fertility is highly questionable especially as the formation of this metabolite is quite different in rats compared to other species. In addition, all potential indication of developmental toxicity noted in the [redacted] study can be either be explained by 1) rat specific reproductive toxicity (e.g. sperm damage due to an rat specific MOA leading to death offspring) with questionable relevance for humans or 2) caused by parental toxicity (reduced body weight of pups). This is also quite intensively elaborated in the document of Givaudan. Studies investigating specifically developmental toxicity are not at hand for para-cymene, nor have effects in other species indicated such effects (e.g. marsupials). The CLH dossier refers several times to the harmonised classification to TBBA and 2-(4-tert-butylbenzyl) propionaldehyde as a justification for the proposal of a Repr.1B for developmental toxicity chosen here. Both substances are classified as Cat. 1B regarding fertility but the aldehyde is classified as developmental Cat. 2 and TBBA is not classified for developmental toxicity at all. Even in the new CLH proposal by the same MS only Cat. 2 is proposed for developmental toxicity for both substances. Although this approach is inconsistent (as the substances are considered to belong to separate groups and to be assessed separately), it supports to some extent that a classification as Repr.1B for developmental effects is not justified for para-cymene via this approach.

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1) ARN Aralkylaldehydes, ECHA September 2022
2) [redacted] 1983).
3) [redacted] (1981)
4) [redacted] (1992)
5) [redacted] (2009).
6) [redacted] (2006).
7) [redacted] (1999)
8) [redacted] (2004)
9) [redacted] (2017)
10) [redacted] (2022)
11) [redacted] (2023)