Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

tetrahydrofurfuryl alcohol

EC Number: 202-625-6

CAS Number: 97-99-4

ECHA/RAC/CLH-O-0000002120-94-03/A2

Adopted

28 November 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.

Substance name: Tetrahydrofurfuryl alcohol (THFA)

EC number: 202-625-6
CAS number: 97-99-4

General comments

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
2012/01/06	Germany / Member State	The German CA notes that on reproduction toxicity only an OECD 421-study (and a range-finding-study) is available for the substance, no higher tier studies (e.g. EOGRTS) exist. In regard of the substance ID we propose to include, if available, the concentration ranges of the main constituent and the impurities.	Noted. As no registration dossier has been submitted at this date for THFA, no reliable information is available to the dossier submitter on concentration ranges of the main constituent and the impurities.	Noted, no further action taken.

Carcinogenicity- No comments received

Mutagenicity- No comments received

Toxicity to reproduction

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
2012/01/09	Norway /Member State	On behalf of the Norwegian Food Safety Authority we submit the following comment. In the range-finding developmental toxicity study in the rat (TSCA, 1992b), reduced mean fetal body weight and an increase in one external malformation (filamentous tail) were reported in the	See attached justification.	As discussed in the Opinion Document, we prefer to take the position of the Dossier Submitter. The available data

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		absence of maternal toxicity. The NOAELs for maternal and developmental toxicity were considered to be 100 and 50 mg/kg/day. Based on these findings, and according to CLP criteria, a classification for reproductive toxicity category 1B is proposed for developmental endpoint.		are limited; it is not possible to conclude reliably that THFA poses such a clear-cut developmental toxicity hazard. However, we agree that Repr 1B is justified, but for effects on fertility and reproductive function.
2012/01/09	Sweden / Member State	The data presented in the dossier is absolutely enough to give clear support for the suggested classification Repr. 2 according to CLP (Repr. Cat 3 according to 67/548/EEC DSD). In addition due to the fact that: • there are severe and lasting effects on the testes testis epithelium • strong effects on number of pups born and total resorption in the higher dose groups. • the effects on testes are seen after exposure via oral, inhalatory and dermal routes. • there is a suspicion about and endocrine mode of action and • the effects must be considered to be relevant for humans SE believes that even a higher classification category (Repro 1B) should be considered. We find the presented data reliable according to standard test guidelines, supported by additional studies. The effects reported are clear and give enough confidence to consider the substance as a reproductive toxicant. We think that additional studies will only further support this. Therefore, we do not see the need to perform additional investigations and risk the use of more experimental animals to provide a higher degree of protection for human health.	See attached justification.	We agree that at least a classification category 2 is justified for fertility/reproductive function and developmental toxicity. We would prefer category 1B for effects on fertility/reproductive function, as discussed in the Opinion Document. It is possible that additional data on developmental toxicity could strengthen the case for a 1B classification for that endpoint.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
2012/01/06	Germany / Member State	The German CA suggests considering a discussion on Repr. 1B for THFA (both for fertility and developmental effects). Marked effects of THFA on reproductive health have been observed in animal studies and we are concerned that Repr. 1B might be the more appropriate classification category for both fertility and development, considering the following points: 1. Potential relevance of uncertainties in the database a) Summaries vs. full study reports We note that taking regulatory decisions on the basis of study summaries instead of full reports is a standard procedure for authorities under the REACH legislation. If a study summary mentions findings relevant for a classification we would not consider these uncertain, as long as there is no reason to believe the summary was inaccurate. In the present case, the summaries have been taken from a high-level risk assessment program and there are no clues suggesting deficiencies in quality. Moreover, the lead registrant under REACH, with access to the full study report (and, potentially, even more information) apparently does not question the findings as portrayed in the study summaries by themselves, but only their meaning under the WoE scheme. Otherwise we would assume they would have seen the need for providing clarification in the form of a more detailed summary or even the full study reports as requested by France. Thus, in our view, the fact that only study summaries were available to ANSES does not appear to compromise the observed findings and should not be used as an argument for assigning Repr. 2 vs. Repr. 1B. b) Limited number of animals and/or assessed parameters in the developmental study and reproductive toxicity screening test	See attached justification.	We have no problem with the type of studies presented or the way in which the information was presented to RAC. There are uncertainties in the data (e.g. relevance of maternal toxicity, effects on hormones, significance of preliminary study showing possible increase in filamentous tail, limited mechanistic understanding, etc) , but we agree with DE that overall there are sufficient grounds to justify a category 1B classification. Our rationale is presented in the Opinion Document.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		We agree that these limitations could be important in the sense that relevant findings could have been overlooked (e.g. with a higher number of animals in the developmental study, tail anomalies might have attained statistical significance In addition, with skeletal/visceral examinations, anomalies other than tail malformations might have been revealed). However, conversely, if marked toxicity with relevance for classification IS observed in such limited studies and, even more so, is observed consistently over several studies (such as embryo/-foetotoxicity and –lethality in the present case) we do not agree that the limitations of the study design should impact on the classification decision in the sense that these findings should be discounted. Adverse effects on sexual function and fertility DE supports a proposal for classification for adverse effects on sexual function and fertility. However, there are as well arguments for Repr. 2; H361f as for Repr. 1B; H360F respectively. A Weight-of-Evidence assessment of the results of the repeat-dose and reproduction/developmental toxicity screening tests does provide some but perhaps not sufficiently clear evidence for an adverse effect on reproductive function, where clear evidence would be required for assigning Repr. 1B acc. to CLP Annex I, Table 3.7.1(a). The effects on reproductive organs (generally slight to moderate histopathological effects in testes and epididymides at the highest dose level with marked reduction of body weight gain) observed in the screening test were consistent with the results in the repeated dose toxicity studies (testis toxicity, however with no specified reduction of brain weight in some studies). On the other hand, no impairment of fertility was reported in the OECD 421 study. This could be seen as evidence against a relevant effect on fertility. Alternatively it could be attributed to limitations in study design (cf. CLP Annex I, 3.7.2.5.2) or to the known lower impact of sperm number/quality on rat reproductive performance as compared to humans.		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Adverse effects on development of the offspring DE considers classification for Repr. 1B; H360D more appropriate based on the high resorption rate (100 %) in rats at a dose level of 500 mg/kg bw (Hirata-Koizumi, 2008). Although effects occurred in the presence of some maternal toxicity including presumably decreased body weight gain and some clinical signs (e.g. increase and decrease in locomotor activity), total resorption in rat is not a nonspecific effect as a consequence of maternal toxicity. Furthermore, inconsistent changes of the locomotor activity without a clear detailed justification are not a convincing indicator for a clear and severe evidence for neurotoxicity. Also, values given for body weight gain during gestation are not the corrected values, so the marked reduction is mostly due to lack of embryos/fetuses. Assuming that no absorption would have occurred at the highest dose level, body weight gain would be at 132 g (assumptions: fetal body weight of 5 g and the number of fetuses (like control) of 14.8) and thus would result in a reduction of body weight gain of 19.5% as opposed to 64 %. As a consequence, we agree with ANSES that the reproductive effects observed with THFA have to be 'considered not to be a secondary non-specific consequence of other toxic effects'. In our understanding of the CLP criteria for reproductive toxicity, the statement in the previous paragraph is a prerequisite for classification vs. non-classification, but NOT a decisive criterion for choosing one category (2 or 1B) over the other. In fact, the CLP regulation appears to be quite straight-forward about when to choose Repro. 2 in such a case, viz. only "when there is mechanistic information that raises doubt about the relevance of the effects for humans". Conversely, in our opinion, the absence of such information for THFA appears to call for classification as Repr. 1B – H360FD.		
2012/01/05	United States Affiliated With	The CLH report proposes reproductive toxicity Category 2 for both fertility and	The disruption of the hypothalamus-pituitary-	We agree that it is not known whether

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
	Organisation / Company-Manufacturer / Pennakem, LLC	developmental toxicity. The data reviewed in the CLH report supports this classification. Within the report, however, it is suggested that the effects on testes in male rats and fetotoxicity seen in reproductive and developmental toxicity studies may be linked to a disruption of the hypothalamus-pituitary-gonadal axis. No data in any of the reviewed studies support such a suggestion. Further, criteria for the conduct of studies appropriate for assessing the impact of chemicals on the hypothalamus-pituitary-gonadal axis support a conclusion that the dose levels causing testicular and fetal toxicity in the reviewed studies were excessive and not relevant to evaluate such endocrine effects. 4 In conclusion, the assessment was reasonable and well conducted. It is recommended, however, that any suggestion of possible hypothalamus-pituitary-gonadal axis effects be removed from the document since this suggestion is neither supportable nor appropriate. Respectively The CLH report includes a comprehensive review of the toxicologic database for THFA. As a result of the review, classification for potential reproductive toxicity has been suggested. Section 4.11.5 (Page 28) Category 2: Fertility H361: The basis for placing THFA in Category 2 for fertility were the results from 2 repeated dose toxicity studies in rats and a reproductive/developmental toxicity study in rats. - These studies demonstrated that the testes are the primary target	gonadal axis was noted in the CLH report only as a hypothesis that could explain some effects observed. This hypothesis was proposed by the authors of the OECD 421 study based on the decreased pituitary weight and the prolonged mean oestrous cycle and gestation lengths. Therefore, we see no reason to delete this sentence in the CLH report. However, we agree that the available dataset did not permit to assess endocrine properties of THFA and thus no conclusion could be done on this issue.	the reproductive effects seen were related to a disruption of the endocrine system or not, and have written the opinion accordingly. Unlike the industry assessment, RAC has considered THFA to have an adverse effect on pregnancy (dystocia). Taking this into account, RAC concluded that the weight of evidence favoured a category 1B classification.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		organ for THFA toxicity. The effects on the testes were primarily noted in the presence of significant systemic toxicity and no adverse effect on reproduction was noted in the reproduction/developmental screening test. However, the RMS felt that the degree of difference in the relative organ weights of the testes suggested a direct effect of compound rather than an effect secondary to systemic toxicity. In addition, the lack of a functional effect on reproduction was considered to be less important in supporting no classification as rats produce sperm in quantities that greatly exceed the minimum required for fertility. - In the OECD 421 the RMS highlighted that the mean oestrus cycle length was prolonged suggesting an effect on the hypothalamus-pituitary-gonadal axis although this was concluded by the authors of the study report to be minimal and of no toxicological significance. Category 2: Developmental Toxicity H361 Classification of THFA in reproductive toxicity category 2 for developmental toxicity was based on the results from the reproductive/developmental toxicity study. At the top dose, early fetal resorption was noted in all dams. At 150 mg/kg early fetal resorption, mummification of fetuses in utero and poor post-natal survival was noted. Additionally, complete fetal resorptions at 1000 and 500 mg/kg , maternally toxic dose levels, and low fetal weights were noted in a range finding developmental toxicity study at 100 mg/kg. A 3 non-statistically significant incidence in filamentous tail was recorded		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		for fetuses at 100 mg/kg. The RMS concluded that "a classification for reproductive toxicity category 2 is also proposed for developmental endpoint considering that the effects were observed in the context of maternal toxicity (decreased body weight) and that the low level of information available from these preliminary studies does not allow to conclude on the potential link between maternal toxicity and developmental effects." The notifier considers that the cannibalism seen at 150 mg/kg is likely due to poor pup survival or health status immediately after birth and is considered to reflect normal behavior of dams rather than abnormal behavior as highlighted by the RMS. Based on the limited amounts of data available the conclusions of the RMS on classification, although conservative, are considered reasonable. Of concern in the CLH report, however, is the implication that the effects seen in the studies, especially in the reproductive study, may be related to a disruption of the hypothalamus-pituitary-gonadal axis. This suggestion was expressed in several sections of the document and elaborated in section 4.11.4. The notifier believes that the reviewed studies do not provide sufficient information to permit such a link between effects seen in the various studies and disruption of the endocrine axis. In the absence of studies which fully evaluate such effects it is considered that: Section 2.2 sentence beginning "the prolongation of the estrus cycle"; Section 4.11.4 paragraph 3,		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Section 4.11.5 paragraph beginning 'In the OECD 421 study' - sentence " the prolongation of the estrous cycle could suggest a disruption of the hypothalamuspituitary- gonadal axis" should be deleted as they are speculative and do not reflect available data. *ECHA comment: The "Conclusion" part of the attached document "**Evaluation of the CLH Report: Proposal for Harmonised Classification and Labelling for Tetrahydrofurfuryl alcohol**" is copied below:* **CONCLUSION** The CLH report proposes reproductive toxicity Category 2 for both fertility and developmental toxicity. The data reviewed in the CLH report supports this classification. Within the report, however, it is suggested that the effects on testes in male rats and fetotoxicity seen in reproductive and developmental toxicity studies may be linked to a disruption of the hypothalamus-pituitary-gonadal axis. No data in any of the reviewed studies support such a suggestion. Further, criteria for the conduct of studies appropriate for assessing the impact of chemicals on the hypothalamus-pituitary-gonadal axis support a conclusion that the dose levels causing testicular and fetal toxicity in the reviewed studies were excessive and not relevant to evaluate such endocrine effects. In conclusion, the assessment was reasonable and well conducted. It is recommended, however, that any suggestion of possible hypothalamus-pituitary-gonadal axis effects be		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		removed from the document since this suggestion is neither supportable nor appropriate. *End of attachment*		

Respiratory sensitisation- No comments received.

Other hazards and endpoints

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
2012/01/05	United States / Affiliated With Organisation / Company-Manufacturer / Pennakem, LLC	Two documents are attached - one is the detailed comments on the toxicity study, the other is an April 2011 endpoint study on the readily biodegradeability of THFA. *ECHA comment: The "Conclusion" part of the attached document "**Evaluation of the CLH Report: Proposal for Harmonised Classification and Labelling for Tetrahydrofurfuryl alcohol**" is copied under the section 'Toxicity to Reproduction'*	Since the CLH report is focusing on toxicity of THFA, the report on the readily biodegradability has been not taken into account.	In agreement with MSCA response.

ATTACHMENTS RECEIVED:

Evaluation of the CLH Report: Proposal for Harmonised Classification and Labelling for Tetrahydrofurfuryl alcohol, Prepared by Vincent J. Piccirillo, 2012. (Final-THFA-response-to-classification-010512.pdf). Submitted by United States / Andrew Nitiss / Affiliated With Organisation / Company-Manufacturer / Pennakem, LLC ***Conclusion part of the attachment is copied under the section "Toxicity to Reproduction".***

Turk, R.S. (2011), **Plant Tissue Dissipation/Uptake of Tetrahydrofurfuryl Alcohol (THFA)** (Plant Tissue Dissipation-Uptake of Tetrahydrofurfuryl Alcohol (THFA).pdf). Submitted by United States / Andrew Nitiss / Affiliated With Organisation / Company-Manufacturer / Pennakem, LLC