Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

tetrahydrofurfuryl alcohol; tetrahydro-2-furylmethanol

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

ECHA/RAC/DOC-O-0000002120-94-03/F

Adopted

28 November 2012

28 November 2012
CLH-O-0000002120-94-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical Name: **Tetrahydrofurfuryl alcohol**

EC Number: **202-625-6**

CAS Number: **97-99-4**

The proposal was submitted by **France** and received by the RAC on **3 December 2010.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP Regulation	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Eye Irrit. 2 – H319	Xi; R36 SCL: Xi ≥ 10%
Proposal by dossier submitter for consideration by RAC	Repr. 2 – H361fd	Repr. Cat 3; R62-63
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Eye Irrit. 2 – H319 Repr. 2 – H361fd	Xi; R36 Repr. Cat 3; R62-63 SCL: Xi ≥ 10%

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at *http://echa.europa.eu/harmonised-classification-and-labelling-consultation* on **25 November 2011**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **9 January 2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Andrew Smith**

Co-rapporteur, appointed by RAC: **Lina Dunauskiene**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **28 November 2012** and the comments received are compiled in Annex 2.The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **tetrahydrofurfuryl alcohol** should be classified and labelled as follows[1]:

[1] Note that not all hazard classes have been evaluated

Classification and labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statemen t Code(s)		
603-061-00-7	tetrahydro-2-furylmethanol; tetrahydrofurfu ryl alcohol	202-625-6	97-99-4	Repr. 1B Eye Irrit. 2	H360Df H319	GHS08 GHS07 Dgn	H360Df H319			

Classification and labelling in accordance with the criteria of DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
603-061-00-7	tetrahydro-2-furylmethanol; tetrahydrofurfuryl alcohol	202-625-6	97-99-4	Repr. Cat 2; R61 Repr. Cat 3; R62 Xi; R36	T R: 36-61-62 S: 2-36/37/39-46	Xi; R36: C ≥ 10%	

SCIENTIFIC GROUNDS FOR THE OPINION

The following opinion relates only to the reproductive toxicity of tetrahydro-2-furylmethanol; tetrahydrofurfuryl alcohol (THFA) since this was the only hazard class reviewed in the proposal for harmonised classification and labelling, as submitted by France.

REPRODUCTIVE TOXICITY

Summary of the Dossier Submitter's proposal

The Dossier Submitter presented data from repeated-dose toxicity and reproductive toxicity studies in animals in support of their proposal. This information is summarised below. The Dossier Submitter noted that full study reports were not available for the repeated-dose toxicity studies, resulting in the information on these studies being collated from an IUCLID dataset compiled for the purpose of the High Production Volume (HPV) Chemicals' Program and an industry position paper; hence, some data were unavailable to the Dossier Submitter.

Repeated dose toxicity studies

The main effects induced by THFA in repeated-dose toxicity studies in rats and dogs are localised in the male reproductive system, and especially in the testes. The findings include decreased testes weights associated with necrosis of the seminiferous tubular epithelium/testicular degeneration and/or an impaired spermatogenesis (decrease in the ratio of the spermatid to Sertoli cells counts, loss of spermatogenic activity, and decrease in mean number of sperm and in mean sperm production rate). Although these effects were clearly observed in rats, the significance of testicular findings is doubtful in dogs since they could be due to sexual immaturity.

The other target organs are the thymus (atrophy) and the spleen (atrophy of the red pulp, decreased extramedullary hematopoiesis and inflammation of the capsule in the spleen) in rats and suggest that THFA could have effects on hematological and/or immunological systems. An effect on the hematological system is supported by the changes in haematological parameters.

In addition to these effects, decreased body weight gains associated with reduced food consumption were observed in all studies at the highest doses, in particular in the male rats. In the 90-day study in rats exposed to THFA by gavage, clinical signs that could indicate neurotoxicity were also reported (increased/decreased locomotor activity, prone position, decreased grip strength).

Reproductive toxicity studies

Two studies are available: an OECD TG 421 (Reproduction/Developmental Toxicity Screening test), dated 2008, and a range finding developmental toxicity test, dated 1992.

In these studies, THFA induced some parental effects including changes in locomotor activity and inhibition of body weight gain associated with reduced food consumption. The decreased body weight observed in females during gestation in both studies could have been due to the loss of embryo/fetuses in these groups and decreased food consumption could have been due to the decreased nutritional requirement accompanied with embryonic/fetal loss. However, it cannot be excluded that decreased body weight gain could be due to a direct effect of THFA since this finding was also observed in some repeated-dose toxicity studies at high dose levels.

In the OECD TG 421 study, the target organs reported in the parental generation were the thymus, spleen, testes and/or the epididymides. Effects in the spleen (incidence of capsule inflammation increased and grade of extramedullary hematopoiesis decreased) and in the thymus (atrophy) suggest that THFA could affect hematological and/or immunological parameters as observed in repeated-dose toxicity studies.

In the testes, seminiferous tubular atrophy and hyperplasia of interstitial cells were observed. The following hypothesis is proposed: THFA might impair the synthesis of testosterone leading to an increased luteinizing hormone (LH) level via negative feedback. This hypothesis is supported by the hyperplasia of interstitial cells which is known to develop with increased LH. Reduced pituitary weight was observed in males and females and could indicate a disruption of the hypothalamus-pituitary-gonadal axis. This is also suggested by the prolonged estrous cycle, however, the degree of change in estrous cycle was slight and most females showed 4 to 5 day estrous cycles. It is unknown whether the disruption of the hypothalamus-pituitary-gonadal axis is secondary to a direct effect on testes or whether the effects on the testes are secondary to a hormonal disruption. It is also noted that an effect on testosterone levels may have an impact on the growth of males, and *vice versa*.

Despite these effects, no effects on reproductive parameters were noted. This could be explained by the fact that rodent males produce sperm in numbers that greatly exceed the minimum requirements for fertility (sperm production could be reduced up to 90 % without affecting fertility in Sprague-Dawley and Wistar rats). Besides, in the OECD TG 421 study, exposure of males is limited to two weeks before mating and it is probably not sufficient to affect spermatogenesis and fertility.

THFA also induced effects on the development of rats. In the OECD TG 421 study, total embryonic loss was noted at 500 mg/kg/day. At 150 mg/kg/day, most females delivered (8/11 pregnant females). Besides, only about half of the dams had pups the next day after parturition and the total number of pups born was markedly decreased. This could be due to cannibalism but may also mask potential resorptions. Cannibalism can reflect either an abnormal behaviour of the dams (possible neurotoxicity of THFA) or behaviour of the dams resulting from a poor health status of the pups (health status of the missing pups unknown). Among the pups born at 150 mg/kg around half of them were dead and half of the pups born alive died before PND 4. In the range-finding developmental study, 100 % incidence of early resorptions was observed at 500 and 1000 mg/kg/day and decreased fetal weight was found at 100 mg/kg/day.

Concerning the incidence of external and internal malformations, there was no difference between control and treated groups in both studies in the range-finding study. However, in the OECD TG 421 study, no skeletal examination was performed and effects on development could not be evaluated at the higher dose since no litter was obtained. In the second study, although not significant, filamentous tail was observed in 5 of 124 fetuses (4 of 8 litters) at 100 mg/kg/day.

Classification rationale

Fertility

When administered to rats, THFA induced effects on sexual organs and function. Testicular atrophy and impaired spermatogenic activity were observed in the repeated-dose toxicity studies (28 and 90 days) and in the OECD TG 421 study. In this latter test, there was no impaired fertility or fecundity, but this could be explained by rodents being able to produce sperm in numbers that greatly exceed the minimum requirements for fertility and/or by the limited exposure of males to THFA before mating. However, the Dossier Submitter also noted that it was possible that the nature of the effect was inherently not severe enough to have an adverse effect on male fertility. Accounting for this uncertainty, in accordance with the criteria, it appeared to the Dossier Submitter that Repro. 2 was the most appropriate CLP classification.

Although the effects on reproductive organs in male rats were generally reported in the presence of decreased body weight, the Dossier Submitter noted that the following findings suggested that they were not secondary to a general toxicity of THFA. This indicated that a proposal not to classify for sexual function and fertility would have been inappropriate.

- Slight necrosis of the seminiferous tubular epithelium of the testes in 2/5 males at 150 mg/kg/day [28-day oral study in rats] in absence of effect on body weight at this dose,
- Adverse effects on spermatogenesis at 300 and 1000 mg/kg bw/day, including a decrease in mean number of sperm in the testis and in mean sperm production rate [90-day dermal study in rats] in absence of effect on body weight at these doses,
- Significantly decreased relative testes weights at 10,000 ppm (≈ 720 mg/kg/day) [90-day oral in rats],
- Decreased epididymides relative weights from 5000 ppm (≈ 360 mg/kg/day) and decreased testes relative weights at 10,000 ppm (≈ 720 mg/kg/day) [90-day oral study in rats],
- Decreased prostate (150 and 500 ppm) and epididymides relative weights (500 ppm) [90 day inhalation study in rats],
- Decreased relative testes and epididymides in males at 500 mg/kg/d [OECD TG 421 study].

The prolonged oestrus cycle seen in treated female rats was only a slight effect and judged not to be of toxicological significance. Although an increased gestation length was seen in the OECD TG 421 study this could not be explained mechanistically and was considered insufficient to justify a higher classification given also that there were no histological findings on reproductive organs and no impaired fertility in females.

In recognition that an impairment of fertility had not been shown with THFA and the limited quality of evidence overall, the Dossier Submitter judged the data not to be sufficiently convincing for a Category 1B classification. A Repr. 2 classification was proposed.

Developmental toxicity

When administered by the oral route to rats, THFA induced effects on development, justifying classification.

An increased incidence of resorption or mummification of foetuses was observed at 150 and 500 mg/kg/day in the OECD TG 421 study and at 500 and 1000 mg/kg/day in the developmental range-finding study. This was associated with decreased total number of pups born, number of live pups on PND 0 and 4, and delivery and live birth index, and an increased number of dead pups on PND 0 in the OECD TG 421 study.

The Dossier Submitter observed that this foetotoxicity occurred in the presence of a maternally toxic effect that resulted in decreased body weight with decreased food consumption and clinical signs. In the range finding developmental study, decreased foetal weight was reported in the absence of maternal toxicity, but the magnitude of this effect was not described adequately. The Dossier Submitter concluded that these effects justified classification but the preliminary nature of the available studies prevented them reaching a clear view on the potential link between maternal toxicity and foetotoxicity.

The Dossier Submitter also noted that information on the potential of THFA to induce skeletal malformations was incomplete, given the relatively small numbers of animals in the test groups and the selectivity of endpoints. The relevance of the increased incidence of filamentous tail seen in the range finding study (4% of foetuses in 4/8 litters at 100 mg/kg) was uncertain. This finding was not statistically significant but no historical control data had been presented to help judge its significance. Accordingly, the Dossier Submitter proposed a category 2 classification for this endpoint.

Comprehensive study reports were not available. Further, the range finding developmental study and the OECD TG 421 study had not provided complete information, due to the relatively small group sizes and selectivity of endpoints (for

example, no skeletal examination was performed in the screening assay). This further limited the case for a higher classification.

Comments received during public consultation

Comments were received from only three Member States (Sweden, Germany and Norway) and from one industry organisation. The Member States that responded all questioned whether a category 1B classification for reproductive toxicity might be more appropriate (Germany only for developmental toxicity). The industry comments were essentially in support of the classification proposed by the Dossier Submitter and were accompanied by an evaluation of the proposal from a US-based consultancy. However, the industry comments queried the mechanistic assessment provided by France.

In response, the Dossier Submitter provided a short document that provided a further analysis of the key information relevant for deciding how to classify this substance for reproductive toxicity.

In summary, the key additional points made by France were as follows.

(i) Fertility – in answer to industry, the available data were insufficient to enable an assessment of the potential of THFA to possess endocrine properties; no conclusion could be reached on this issue.

(ii) Developmental toxicity (OECD TG 421 study) - the decreased body weight of dams in treated groups during gestation could have been due to the lack of embryos/foetuses or a direct maternally toxic effect of THFA, it was not possible to make a more complete assessment from the available data.

(iii) Developmental toxicity (OECD TG 421 study) - it was not possible to explain the loss of pups after parturition. The apparent cannibalism by the dams could have been due to poor pup health status and/or an abnormal behaviour of the dams themselves.

(iv) The 4% incidence of filamentous tail (an external malformation) appeared to have been above relevant historical values (maximum value found in the literature was 0.36%), but definitive data for the relevant strain of rat were lacking.

The RAC assessment and comparison with the classification criteria

As indicated by the nature of the comments received from Norway, Sweden and Germany, the RAC observes that the available information could be interpreted to justify either Repro. 2 or 1B classifications for effects on fertility/sexual function and development. Given the absence of human data, and no known resemblance of THFA to substances known to cause reproductive toxicity in humans, no case for a category 1A classification can be made.

Sexual function and fertility

The findings in the male rat reproductive system following treatment with THFA justify classification for fertility. However, as noted by the Dossier Submitter and in the comments received during the public consultation from Germany, the effects seen were generally slight to moderate and occurred at high doses (from 150 mg/kg/day when administered for 28 days and from 300 mg/kg/day when administered for 90 days), mostly alongside a marked reduction in body weight gain; no such adverse effects were reported with doses below 150 mg/kg/day, and, likewise, at these doses systemic toxicity was not reported. The adverse effects on the male rat reproductive system were therefore usually only observed at doses that also resulted in systemic toxicity. The severity of the effects did not increase with increased duration of the study. Because of deficiencies in the study design, the finding of testicular toxicity in dogs was not sufficiently robust evidence on which to base a classification decision. No impairment of fertility was observed in the OECD TG 421 study, which could be interpreted as evidence that THFA does not possess this hazard. However, it should be considered that the study

may have been insufficiently designed to detect such an effect (exposure to THFA was limited to two weeks before mating), and that rats have a large functional reserve in sperm numbers compared to humans; therefore, some uncertainty is connected with this negative finding in relation to possible adverse effects in humans.

There is also the observation of increased gestation duration in the OECD TG 421 study to take into account (mean value of 24.7 days at 150 mg/kg/day THFA, compared with 22.6 days in controls). Vaginal haemorrhage was seen in the late gestation period in 1/11 pregnant dams at 150 mg/kg/day and 2/12 pregnant dams at 500 mg/kg/day that did not deliver their pups or experienced total litter loss; however, this effect may have been caused by haemotoxicity, as observed in the repeated dose studies (decrease in mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocyte and platelet counts and prolongation of prothrombin time in males and females; decrease in reticulocyte count in males and haemoglobin concentration in females). Apart from this, signs of abnormal or difficult parturition (which would be indicative of dystocia) were not described. Notwithstanding, this marked effect in delaying the onset of parturition could have been a factor in the poor survival of pups at or around the time of birth. No clear mechanistic basis for the effect has been provided, and RAC considered that it was unlikely to be purely a secondary consequence of maternal toxicity. This provides evidence of an adverse effect on pregnancy and, as such, also comes into the scope of this classification endpoint.

Developmental toxicity

A high level of foetotoxicity was seen in rats exposed to THFA. In the OECD TG 421 study, a 100% resorption rate at 500 mg/kg was reported. At 150 mg/kg/day, the delivery index[1] and the live birth index[2] were significantly reduced (46.4 and 43.1, respectively). At this dose, 5/11 dams did not have any pups the next morning, with no concrete explanation for this, although cannibalisation by the dams was hypothesised. The RAC considered the potential influence of maternal toxicity, as indicated by decreased maternal weight gain, on the observed foetotoxicity. The resorptions were reported to be early, indicating that they had occurred on or before day 14 of gestation. Up to this time, maternal body weight was only slightly affected at 500 mg/kg/day (≤ 10%) and so does not provide an explanation for the 100% resorption at this dose. The overall body weight gain reduction of 64% in these dams was judged by RAC to have been accounted for, to some extent, by the embryonic loss, although information on the body weight gains adjusted for uterine weights was not available. At 150 mg/kg/day, early resorption was recorded in one dam, without THFA having an effect on body weight up to and including day 14. The overall body weight gain during gestation was reduced by 30% at this dose, but, based on a comparison of the weight loss that occurred during parturition in the controls and the dams at 150 mg/kg/day, and considering that the groups had similar numbers of implantation sites, this may have been at least partially explained by foetotoxicity. This interpretation of the data is supported by the oral rat repeated-dose studies, in which body weight gain of females was unaffected at doses up to 600 mg/kg/day for 28 days and 460 mg/kg/day for 90 days. The other noted maternal toxicity at 150 and 500 mg/kg/day comprised increased or decreased locomotor activity, vaginal haemorrhage (as reported above), transiently decreased food consumption and extramedullary haematopoiesis. RAC concluded that the maternal toxicity did not account for the marked level of embryo/foetotoxicity observed.

A one hundred per cent incidence of early resorption was also reported in the range-finding developmental study at doses of 500 and 1000 mg/kg/day. At these doses, a decreased maternal body weight gain was recorded from gestation day 8, with increased statistical significance throughout the rest of the study; the magnitude of the changes was not reported, but they were associated with reduced food consumption. The body weight gain of female rats was statistically significantly decreased at 925 mg/kg/day (but

[1] Delivery index = total number of pups born / number of implantation sites x 100
[2] Live birth index = number of live pups on PND 0 / total number of pups born x 100

not at 460 mg/kg/day) in an oral 90-day repeated dose study, suggesting that the effect on maternal body weight at 1000 mg/kg/day was indicative of maternal toxicity. Other signs of maternal toxicity were impaired mobility, decreased muscle tone, absence of pain response and exophthalmus of both eyes. An additional finding in this study, not reported in the OECD TG 421 study, was a decreased foetal weight at 100 mg/kg/day in the absence of a decreased maternal body weight gain; however, it was not possible to judge the severity of this effect, as the values were not given. The increased incidence of filamentous tail in rat pups is regarded as a serious lesion and the observed incidence rate in the range-finding developmental toxicity study was above the historical values reported for control rats generally. It should be noted, though, that historical values for the relevant rat strain were not available. Furthermore, the increases were not statistically significant. This casts some doubt on the toxicological significance of the finding.

Conclusion

The only available studies that specifically investigated the reproductive toxicity of THFA were a reproduction/developmental toxicity screening study and a range-finding developmental study. Although several repeated dose toxicity studies were available, the Dossier Submitter did not have access to the study reports for these. The data on which RAC has based its assessment was therefore limited. Notwithstanding, THFA had a clear and severe effect on reproductive toxicity that merits classification for both fertility/sexual function and development. The question is whether category 1B or 2 for each effect is the more appropriate.

The testicular effects seen in rats were generally not severe and occurred at doses that also caused general toxicity (evident as impacts on body weight gain). However, the effects on pregnancy (delayed onset of parturition) did potentially have serious consequences and the mechanistic basis for these effects is not well understood. In particular, it is not known if administration of THFA had a direct effect on parturition mechanisms, or if the presence of dead foetuses in the uterus resulted in the delay of parturition. If it were the latter, the concern for an adverse effect on sexual function / fertility would be lessened and the predominant concern would be for a developmental effect.

THFA resulted in complete early resorptions at doses of 500 and 1000 mg/kg/day; RAC concluded that those that occurred at 500 mg/kg/day, at least, could not be sufficiently explained by maternal toxicity. There are different possible interpretations of the finding that, the morning after delivery, some of the dams at 150 mg/kg/day did not have any pups: the pups may have been dead for a while before parturition commenced, resulting in cannibalisation by the dams; or resorptions may have accounted for some of the reductions in pup numbers; or, alternatively, the delay in the onset of parturition may have resulted in pup death shortly before or during parturition or poor status after birth. The other observed developmental effects, foetal weight reduction (magnitude not known) and the increased incidence of filamentous tail, were of uncertain toxicological significance.

Based on the limited information available, it is difficult to decide if separate mechanisms were involved in the foetotoxicity and the delay in the onset of parturition. However, RAC's interpretation of the data is that the main concern is the potential for a direct effect on embryos / foetuses rather than a maternal effect that impacts on parturition. CLP states that '*the major manifestations of developmental toxicity include (1) death of the developing organism*…' It was undoubted that complete embryonic loss occurred at 500 mg/kg/d and that this was neither sufficiently explained by maternal toxicity nor by effects on parturition. It is the RAC's opinion that the severity of the effect provided clear evidence of an adverse effect on development and that, therefore, the criteria for category 1B for this end-point are met.

The findings at 150 mg/kg/day are more difficult to assign to either sexual function/fertility or developmental toxicity, but in the absence of information to the

contrary the RAC concludes that they were probably linked. Despite this, the evidence of an effect on parturition/pregnancy outcome together with testicular toxicity indicates that a classification for sexual function/fertility is justified. Since the quality of the evidence is less convincing than that for developmental toxicity and is associated with uncertainties, category 2 would seem to be the appropriate classification.

In conclusion, based on some evidence for effects on parturition and pregnancy outcome and testicular toxicity, RAC is of the opinion that classification in category 2 for fertility and reproductive function is justified. Based on total early resorptions and foetotoxicity, RAC concludes that THFA fulfils the criteria for developmental toxicity, category 1B.

CLP Regulation
Repr 1B; H360Df (May damage the unborn child) (Suspected of damaging fertility)

DSD
Repr Cat 2; R61 (May cause harm to the unborn child)
Repr Cat 3; R62 (Possible risk of impaired fertility)

ANNEXES:

Annex 1 Background Document (BD), gives detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)