Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

tetrahydrofuran

ECHA/RAC/DOC No CLH-O-0000000954-69-03/F

Adopted

25 May 2010

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

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

Substance Names: ***Tetrahydrofuran***

EC Number: 203-726-8

CAS Number: 109-99-9

The proposal was submitted by France.
The proposal was received by RAC on 20 August 2009.

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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp on ***2 September 2009***. Parties concerned and MSCAs were invited to submit comments and contributions by ***17 October 2009***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Andrew Smith***
Co-rapporteur, appointed by RAC: ***Lina Dunauskiene***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***25 May 2010,*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2

The RAC Opinion was adopted by ***consensus.***

OPINION OF RAC

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

Classification & Labelling in accordance with the CLP Regulation:	
Classification[3]:	Flam. Liq. 2 – H225 (already listed on Annex VI)
	EUH 019 (already listed on Annex VI)
	Eye Irrit. 2 – H319 (already listed on Annex VI)
	STOT single 3 – H335 (already listed on Annex VI)
	Carc. 2 – H351
Specific concentration limits:	
Conc. ≥ 25%	Eye Irrit.2; H319 STOT SE 3; H335 (already included in Annex VI entry)
M-factors:	none
Notes:	none
Labelling:	GHS02, GHS07, GHS08 Dgr H225, H319, H335, H351

Classification & labelling in accordance with Directive 67/548/EEC	
Classification[2]:	F; R11-19 (already listed on Annex VI)
	Xi; R36/37 (already listed on Annex VI)
	Carc. Cat. 3; R40
Specific concentration limits:	
Conc. ≥ 25%	Xi; R36/37 (already included in Annex VI entry)
Notes:	none
Labelling:	F; Xn; Xi R11-19-36/37-40 S: (2-)(13-)16-29-33-36-37(-46)

SCIENTIFIC GROUNDS FOR THE OPINION

In accordance with Article 115 of REACH and Article 36 (i) of the CLP Regulation, the Committee for Risk Assessment formed an opinion on the harmonised classification of THF relating to the endpoints of mutagenicity and carcinogenicity only. For reproductive toxicity

[1] Note that not all hazard classes have been evaluated
[3] This section should reflect all relevant entries for the C&L: classification, R-phrases, S-phrases, concentrations limits, nota.

and respiratory sensitisation no data were available and therefore the Risk Assessment Committee did not evaluate these endpoints.

The original classification proposal submitted by France included the following rationale for assessing other endpoints.

"Relevant acute and repeated toxicity and mutagenicity data were also reported in this dossier to allow a better understanding of the toxicological profile of THF in relationship with the assessment of its CMR properties. When relevant, potential classifications for endpoints other than CMR are discussed in the proposal to take advantage of having the information available to the competent expert group".

The opinion therefore relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by France.

Carcinogenicity

THF does not appear to be a genotoxic substance and there are no epidemiological reports available to suggest that it may cause cancer in humans. However, the current concern about its potential carcinogenicity stems from the results of a standard 2-species carcinogenicity study reported by the US national Toxicology Program about 12 years ago. Following long-term inhalation THF exposure, there was evidence of carcinogenic activity in male rats for renal tubule epithelial adenoma and carcinoma, but no evidence of carcinogenic activity in females. However, more recent expert pathological analyses of the same original data have indicated that the lesions previously identified as carcinomas were probably adenomas. A marginal increase in mammary gland fibroadenoma was also seen in female rats in the NTP study. In mice, there was no evidence of carcinogenic activity in males, but increased hepato-carcinogenicity was seen in females.

In the rat study, survival at the end of the 2-year exposure period was generally low, with that in the high-dose group (6/50) being lower than in the control group (12/50 controls). The clinical signs and body weights of these two groups were reported to be similar, and so the highest exposure level of 5.4 mg/L did not appear to be an excessively toxic concentration.

Although the THF exposure-related increase seen in male rat kidney tumours was small, it was judged by RAC to have been indicative of a carcinogenic effect. In recent work, a group of expert pathologists commissioned by the US Synthetic Organic Chemical manufacturers Association re-analysed the key data. They focussed on the possibility that regenerative processes associated with severe chronic progressive nephropathy or low-grade α 2u-globulin nephropathy likely contributed to the formation of renal tumours in the exposed animals. These pathologists considered that neither of these mechanisms would pose a "risk" to humans. RAC, however, found that definitive evidence for either of these 2 non-genotoxic mechanisms being involved was lacking. It was therefore not possible to dismiss this carcinogenic hazard in considering the classification of THF.

The trend towards a greater incidence of mammary gland fibroadenoma in female rats following exposure to THF was statistically significant, whereas a similar trend in males was not. However, the incidence of this tumour in the female control group was high, and pair wise statistical comparisons with exposure groups were not significant. This concurrent control incidence of mammary gland fibroadenoma was outside the NTP's historical control range for the same strain and species. Taking into account all these factors, RAC did not find

the evidence for a significant carcinogenic effect of THF in the mammary gland of rats to be convincing.

The only tissue that showed evidence of increased tumour incidence in mice was the liver, in which there was a trend towards an increased incidence of hepatocellular adenoma/carcinoma with increasing exposure in females. These tumours occurred in the absence of an obvious hepatotoxic effect and at a concentration that did not result in clinical signs of toxicity. However, although the mode of action for induction of the tumours has not been clarified, the tumours occurred in the highly sensitive B6C3F1 strain of mouse. As THF is non-genotoxic, and no increases in liver tumours were seen in exposed rats, RAC concluded that the findings were most likely to have been specific to the strain and species tested.

As there is no epidemiological evidence regarding the carcinogenicity of THF to humans, a classification in Category 1a (CLP Regulation), [Category 1 (Directive 67/548/EEC)] is not appropriate.

Although evidence for carcinogenic responses was found in both rats and mice, the tumour types found were largely benign in nature, sex-specific and occurred at a low incidence rate. There are significant doubts about the relevance to humans of all the experimental tumour findings and, given that THF is non genotoxic, classification in Category 1b (CLP Regulation), [Category 2 (Directive 67/548/EEC)] is also judged inappropriate.

Looking specifically at the criteria for deciding between Category 2 (CLP Regulation), [Category 3 (Directive 67/548/EEC)] and no classification, RAC concluded that the findings in relation to kidney tumours in THF-exposed male rats were sufficient to justify classification. The possible mechanism(s) of kidney tumour formation had not been identified clearly, and so there remained uncertainty about extrapolation to humans. Also, such neoplasms are not well known to occur in male Fischer 344 rats spontaneously with a high incidence.
The B6C3F1 strain of mouse has been well established as sensitive to liver tumour induction, and no other tumour type was detected in this species. Consequently, in accordance with the criteria, the liver tumour findings would not in themselves justify classification of THF. However, the absence of increased kidney tumours in the exposed B6C3F1 mice does not detract from the findings in male rats.
Overall, therefore, RAC concluded that THF meets the criteria for carcinogenicity classification in Category 2 (CLP Regulation), [Category 3 (Directive 67/548/EEC)].

In consideration of label to accompany the classification, although the carcinogenic findings were in inhalation studies, there are no significant grounds to indicate the concern is limited to this route of exposure.

The RAC opinion on carcinogenicity takes into account additional pathological analyses of the kidney lesions seen in male rats that were provided by CEFIC during the public consultation. Both France and RAC recognised that these data helped to clarify the nature of the lesions seen in the carcinogenicity study. The data also contributed to RAC's understanding of the mechanistic basis of the kidney tumour findings. RAC also noted that CEFIC were of the opinion that THF should not be classified for carcinogenicity.

Mutagenicity
In the absence of any clear evidence for mutagenicity either in vivo or in a number of in vitro tests, RAC agreed with the proposal of France that no classification is warranted for this endpoint. No information opposing the proposal was received during the public consultation.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[3]
Annex 2	Comments received on the CLH report and response to comments provided by the dossier submitter and the RAC (co-)rapporteurs (excl. confidential information)

[3] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal.