Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

8:2 Fluorotelomer alcohol (8:2 FTOH)

EC number: 211-648-0
CAS number: 678-39-7

CLH-O-0000002460-84-03/F

Adopted

06 March 2013

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CLH-O-0000002460-84-03/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 names: 8:2 Fluorotelomer alcohol (8:2 FTOH)

EC number: 211-648-0

CAS number: 678-39-7

The proposal was submitted by **Norway** and received by the RAC on **17/04/2012.**

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	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	None	None
Original proposal by dossier submitter for consideration by RAC	Repr. 1B; H360D	Repr. Cat. 2; R61
Amended proposal by dossier submitter for consideration by RAC following public consultation	None	None
Resulting harmonised classification as proposed by the dossier submitter (future entry in Annex VI, CLP Regulation)	Pictogram: GHS08; Signal word: Danger (Dgr) Hazard statement code: H360D	Class of danger: Toxic (T); R61

PROCESS FOR ADOPTION OF THE OPINION

Norway 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 **17/04/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **01/06/2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Bert-Ove Lund**

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 reached on **06 March 2013** 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 **8:2 Fluorotelomer alcohol** should be classified and labelled as follows:

Classification & Labelling in accordance with CLP:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
	3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecan-1-ol	211-648-0	678-39-7	-	-	-	-	-	-	-

Classification & Labelling in accordance with DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecan-1-ol	211-648-0	678-39-7	-	-	-	-

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

FTOH is metabolised into PFOA in all mammalian species studied, and as PFOA has recently been proposed by the RAC to be classified for reproductive toxicity (Cat. 1B; CLP), the Dossier submitter (DS) proposes to classify FTOH based on the formation of a metabolite (i.e. PFOA) which is a reproductive toxicant.

According to the Dossier submitter, it is clear that there are species differences in the metabolism of FTOH which makes direct species comparisons difficult. The *in vivo* metabolism of FTOH is faster in mice than in rats, but PFOA is a major metabolite in both species. The half-life of PFOA in both species is in the order of hours to weeks, with the shortest half-life in female rats. *In vitro* experiments have shown formation of PFOA from FTOH in mouse, rat, and human hepatocytes, with the rate of PFOA formation possibly being 5-fold and 12-fold lower in human hepatocytes than in rat and mouse hepatocytes, respectively.

However, although the rate of PFOA formation is slow in humans, the very long half-life of PFOA in humans (3.8 years) will contribute to bioaccumulation of PFOA in humans, and thus to risks for reproductive effects of PFOA.

The notion that metabolism of 8:2 FTOH to PFOA is a relevant mechanism for reproductive toxicity of 8:2 FTOH is supported by FTOH having similar, albeit less severe, effects as PFOA on rat reproduction. A one–generation study on a mixture of FTOHs (27% 8:2 FTOH) in rats showed a dose-dependent decrease in litter size and number of live pups per litter at postnatal day (PND) 0 and 4. The effects were statistically significant from the dose level of 100 mg/kg bw/day (litter size -16%, number of live pups per litter -23% and -26% at PND 0 and 4, respectively), in the absence of any signs of maternal toxicity.

Comments received during public consultation

Comments were received from six Member states and three industry organisations. Among the Member States, two supported the proposal, two disagreed with the proposal, and two didn't express a clear position. Three comments focused on the need for a more detailed evaluation of the kinetics, and two comments suggested considering whether also classification for effects via lactation would be warranted. The three industry organisations disagreed with the proposal, based on e.g. that PFOA is a minor rather than major metabolite of 8:2 FTOH, that the read across criteria of the guidance documents is not followed, and that there is no evidence that PFOA actually accumulates with age in humans.

Assessment and comparison with the classification criteria

There are two developmental toxicity studies and one one-generation study available for FTOH, although one study concerns 8:2 FTOH and the two other studies concern a mixture of FTOHs containing 27% 8:2 FTOH. The exact composition of other FTOHs in the mixture is not known. However, based on the similar toxicological effects of 8:2 FTOH and the FTOH mixture, both with regard to reproductive toxicity and repeated dose toxicity, it is assumed that all these studies can be used to inform about the toxicity of 8:2 FTOH.

The 8:2 FTOH rat developmental toxicity study showed severe maternal toxicity at 500 mg/kg bw/day, including 23% maternal mortality, and effects at that dose level (delayed bone ossification) are therefore not relevant. At 200 mg/kg bw/day, a statistically significant increase in skeletal variations was noted, which is not considered adverse in the context of classification.

In the rat developmental toxicity study on the FTOH mixture, increased foetal skeletal alterations were observed at 500 mg/kg bw/day in the presence of slightly decreased male foetal weight and a 5% reduction in maternal body weight. Overall, these effects are not sufficiently adverse to warrant classification.

The one-generation study in rats of the FTOH mixture (containing 27% 8:2 FTOH), showed a roughly dose-dependent decrease in litter size (14.7, 13.4, 12.4, and 12.5) and number of live pups per litter at birth (14.6, 13.2, 11.3 and 12.1) and at lactation day 4 (14.6, 12.9, 10.8, 11.8) in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively. The effects were statistically significant from the dose level of 100 mg/kg bw/day (litter size -16%, number of live pups per litter -23% and -26% at PND 0 and 4, respectively). It is, however, noted that the effects at 250 mg/kg bw/day are not more severe than at 100 mg/kg bw/day, raising some questions about the dose dependency. The overall good consistency between the other dose groups still speaks in favour of a substance-related effect on development. Furthermore, FTOH is rather rapidly metabolised, and if the toxicity is related to the metabolites, it is possible that saturation of metabolism probably will occur at high dose levels. At 250 mg/kg bw/day, a statistically significant reduction in pup weights on PND 4, 7, 14, and 21 was reported, that was 74-78 % of control values on PND 21 in males and females. After clarifications from the Dossier submitter, the RAC concludes that there were no signs of maternal toxicity at 100 and 250 mg/kg bw/day.

The decreased litter size (-16%) and impaired early survival of the pups that occurred in the absence of any maternal toxicity provide some evidence of developmental toxicity and constitute a borderline case for classification in category 2.

The CLP criteria state that a substance should be placed in Category 2 as a 'Suspected human reproductive toxicant' when the data provide;

"*…some evidence from humans or experimental animals, possibly supplemented with other information…..on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.*

Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects".

The arguments for classification are that a decreased litter size and impaired pup survival (in the absence of maternal toxicity) are very serious effects, whereas arguments against are that the dose-response could be more convincing and that the critical study is conducted on a FTOH mixture (containing 27% 8:2 FTOH) and not on 8:2 FTOH itself. Overall, the RAC is of the opinion that the evidence for reproductive toxicity of this FTOH-mixture is possibly border-line sufficient for classification, <u>but does not think that a study on a commercial FTOH mixture (containing 27% 8:2 FTOH) can be used as the basis for classifying 8:2 FTOH.</u>

In addition, there is a study in mice with an unusual study design that has been considered by the RAC. Pregnant animals were dosed once by gavage with 30 mg/kg bw/day 8:2 FTOH on gestation day (GD) 8. On the day of birth, pup mortality was slightly, but statistically significantly increased, with 31% of the dams having at least 1 (mean 1.4) non-viable pup versus 0% in controls (average litter size 13$\underline{+}$2). The study may indicate toxicological effects by 8:2 FTOH, but because of the design and the slight effects, the results are not sufficiently robust for classification.

Regarding the metabolism of FTOH into PFOA, the RAC notes the large species differences with respect to metabolism and excretion of these substances hampering comparisons. Information on the *in vivo* metabolism of FTOH to PFOA in humans is not available. *In vitro* studies on hepatocytes from different species indicate that humans are slower in the formation of PFOA from 8:2 FTOH than rodents. On the other hand, PFOA has a half-life in

humans in the orders of years, whereas the half-life in rodents is in the order of hours-weeks, showing that the potential for building up high concentrations of PFOA (once formed) in the body is very high in humans as compared to in rodents. The question is whether the formation of PFOA is sufficiently high to warrant a classification based on the developmental toxicity of PFOA (see the RAC opinion on classification of PFOA at http://echa.europa.eu/documents/10162/e7f15a22-ba28-4ad6-918a-6280392fa5ae).

The CLH dossier describes two reports where the metabolism of 8:2 FTOH has been studied in hepatocytes. Martin *et al.* (2005) showed that 1.4% of the available 8:2 FTOH (18 µM) was transformed in 4 hours into PFOA in rat hepatocytes (kept in open flasks). Nabb *et al.* (2007) showed that 0.24% of the available 8:2 FTOH (20 µM) was transformed in 2 hours into PFOA in rat hepatocytes (kept in closed vials). It is noted that 18-20 µM are rather high concentrations, and that the use of lower concentrations potentially could have resulted in a higher percentage of formed PFOA. However, Nabb *et al.* (2007) state that this concentration is below metabolic saturation, but no data is presented. These studies indicate that the formation of PFOA in rat hepatocytes may be in the order of 1%.

Nabb *et al*. (2007) have also compared the metabolism of 8:2 FTOH between rat, mouse and human hepatocytes. It should be noted that rodent hepatocytes were freshly prepared from young animals, whereas the human hepatocytes were purchased frozen and obtained from only three rather old men (54, 68, and 80 years of age). It is also noted that when comparing metabolism at 30 minutes and 2 hours, rats and mice had formed much more PFOA after 2 hours than after 30 minutes (2.4 and 5.6-fold, respectively), whereas the human hepatocytes had only formed slightly more PFOA (1.3-fold). However, cell viability was > 85% in all preparations.

The metabolic rates in rat and human hepatocytes were compared by Nabb *et al.* (2007) in different ways, indicating a 5-fold higher capacity in rat than in human hepatocytes based on metabolism expressed as pmol formed PFOA/min/10^6 cells, a 12-fold difference based on molar concentrations detected at the end of the incubation, or a 9.5-fold difference when hepatocyte metabolism had been converted into whole body capacity. When comparing human and mouse hepatocytes, the difference becomes slightly more than 2-fold higher than above, e.g., a 12-fold higher capacity in mouse than in human hepatocytes based on metabolism expressed as pmol formed PFOA/min/10^6 cells.

It is concluded by the RAC that the data is too limited as a basis for quantitative comparison. Based on the available information, it might seem that the formation of PFOA from 8:2 FTOH in rat hepatocytes is in the order of 1%, and that the corresponding rate in humans might be 5-fold lower, i.e. in the order of 0.2%. However, whereas PFOA is rather quickly excreted in rodents, the half-life in humans is in the order of years.

Read across based on "common significant metabolites" is a valid reason for classification (CLP guidance V3.0, section 1.4.3), but there is no quantitative guidance for how much hazardous metabolites that need to be formed to trigger classification. Although not comparable, it is noted that the generic concentration limits of ingredients of a mixture classified as reproductive toxicants are 0.3% (cat 1) or 3% (cat 2).

Based on comments in the public consultation, a comparison has been made between serum concentrations of PFOA in mice exposed to either 8:2 FTOH or PFOA (see supplemental information below). A 6-fold higher dose of 8:2 FTOH than of PFOA gave a PFOA-concentration 1/10 of that measured in the PFOA-exposed mice after a single administration, possibly indicating that a 60-fold higher dose of 8:2 FTOH than of PFOA has to be administered to mice to give similar serum concentrations of PFOA.

When extrapolating this information to humans, it has to be considered that

- human formation of PFOA from 8:2 FTOH seems to be slower than in mice,
- but that the half-life of PFOA in humans (years) is much longer than in mice (weeks).

Based on the hepatocyte studies, and assuming that the hepatocyte experiments are

relevant as indicators for the *in vivo* formation of PFOA from FTOH, the human metabolism may be 1/12 of the metabolism in mice, whereas the half-life in humans may be 50-fold longer than in mice.

Although PFOA is likely to be formed *in vivo* from 8:2 FTOH, the amount formed is too small to warrant classification. Thus, in mice a 60-fold higher dose of 8:2 FTOH than of PFOA has to be administered to give similar serum concentrations of PFOA after single administrations. When extrapolating to humans, the RAC believes that the very slow rate of metabolism to PFOA in humans is more important than a long half-life of PFOA in humans and that accordingly, one cannot assume that 8:2 FTOH will exert any toxicity in humans via formation of PFOA. The proposal to classify 8:2 FTOH for reproductive toxicity with Repr. 1B, H360D, is thus not supported by the RAC. There are indications of developmental toxicity from the commercial FTOH containing 27% 8:2 FTOH, but as it is not known which components that are responsible for the effects, this data has little impact on the classification of 8:2 FTOH. Overall, the RAC is of the opinion that the available data does not permit classification of 8:2 FTOH for reproductive toxicity.

References:

Fenton SE, Reiner JL, Nakayama SF, Delinsky AD, Stanko JP, Hines EP, White SS, Lindstrom AB, Strynar MJ, Petropoulou SS. (2009). Analysis of PFOA in dosed CD-1 mice. Part 2: Disposition of PFOA in tissues and fluids from pregnant and lactating mice and their pups. Reproductive Toxicology 27 (2009) p. 365-372.

ANNEXES:

Annex 1 Background Document (BD) gives the 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 RAC (excl. confidential information)