Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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/A2

Adopted

06 March 2013

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

Substance name: 8:2 Fluorotelomer alcohol (8:2 FTOH)
EC number: 211-648-0
CAS number: 678-39-7
Dossier submitter: Norway

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
25/05/2012	Germany		MSCA	1

Comment received

In general Germany supports a weight of evidence approach of the Norwegian CA. However, we think that the justification for a developmental toxicity classification for FTOH should be revised and extended. More emphasis should be put on the question whether the metabolism of FTOH to PFOA in mice and humans is a major pathway and results in those PFOA blood levels which have been shown to be essential / necessary to trigger the developmental toxicity observed in the oral mice studies with APFO.

Dossier Submitter's Response

Thank you for your comments. We have included all available data. Concerning blood levels see response to comments from Sweden (comment no. 9).

RAC opinion

The RAC is of the opinion that there is, at present, not sufficient metabolic information to support that PFOA is a major metabolite likely to exert reproductive toxicity after exposure to 8:2 FTOH.

Date	Country	Organisation	Type of Organisation	Comment number
29/05/2012	Germany	TEGEWA	Industry or trade association	2

Comment received

Comments on the proposed classification (March 2012) of 8:2 FTOH for developmental toxicity Points
1. The identified uses of 8:2 FTOH are wrong
2. No agreement to 8:2 FTOH classification proposal

1. Page 13 (Section 2.2) 8:2 FTOH Identified Uses

The information in the CLH Proposal's identified uses is wrong and misrepresents the use of 8:2 FTOH.

The following text correctly describes the uses of 8:2 FTOH:

8:2 FTOH is used as a raw material (one component in a mixture of fluorotelomer alcohols) to manufacture surfactant and polymeric products that have a range of commercial uses (Kissa, 2001; Rao and Baker, 1994). The polymers are used in the treatment of textiles, paper and carpets to achieve oil, stain and water repellent properties. 8:2 FTOH may be present in small amounts in

surfactant and polymeric products that are made with it as a residual unreacted raw material (Dinglasan-Panlilio and Mabury, 2006; Larsen et al., 2006). Articles treated with products made from 8:2 FTOH that contain it as a residual unreacted raw material may have measureable levels present (Berger and Thomsen, 2006).

2. Page 6 (Section 1.3) 8:2 FTOH classification proposal

TEGEWA does not agree to the classification proposal. Existing developmental toxicology study data do not support the classification proposal; on the contrary these data support no classification. The existing data are sufficient for the hazard assessment. Read across to PFOA is not necessary and not in compliance with a required scientific justification specified by both OECD and ECHA. There is great concern that the ECHA technical guidance has not been followed as is required.

Dossier Submitter's Response

1. Thank you for your comments.
2. Please see response to comments from DuPont (comment no.10)

RAC opinion

See comment no 10

Date	Country	Organisation	Type of Organisation	Comment number
31/05/2012	United Kingdom	HSE UKCA	MSCA	3

Comment received

Section 1.3 and 'labelling' below table 4 should also propose S phrases based on the DSD criteria, since these are included in the Annex VI entry. Based on the proposed classification for Repr. Cat. 2; R61, we would suggest the following:

S35-36-37-45-53

Section 2.2. The summary states that the classification proposal is based on read-across to the metabolite of 8:2 FTOH, PFOA. RAC's opinion on PFOA was itself based on read-across to its salt, APFO. Therefore the proposal for classification of FTOH is actually based on read-across to APFO. For clarity, this should be explained in this section.

Dossier Submitter's Response

Thank you for your comments.

We agree with the proposed S-phrases.

The proposal is based on a weight-of–evidence determination, but not on a category approach like read-across (see also response to comment no. 10).

PFOA is used as a group name for PFOA and its salts, and PFOA is mainly produced and used as its ammonium salt, ammoniumpentadecafluorootanoate (APFO, CAS Number: 3825-26-1).
No studies on the human health hazard of PFOA are performed. Most of the studies are performed with APFO. APFO and PFOA are sometimes used interchangeably as both PFO-anion and PFOA (neutral species) exist in solution. Therefore we think it is appropriate to refer to the group name PFOA in this context.

RAC opinion

The comment on PFOA vs APFO is formally correct, but the use of PFOA in the dossier is acceptable considering that PFOA is the most commonly used name for this group (PFOA and its salts).

Date	Country	Organisation	Type of Organisation	Comment number
01/06/2012	France	MSCA	MSCA	4

Comment received

France supports the classification proposal in Repr. 1B; H360D for the reproductive toxicity.

Dossier Submitter's Response
Thank you for the support.
RAC opinion
The support is noted.

CARCINOGENICITY - no comments received

MUTAGENICITY no comments received

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
25/05/2012	Netherlands	RIVM Bureau REACH	MSCA	5

Comment received

Reproductive toxicity
The Netherlands does not agree with the proposal for classification of 8:2 FTOH for developmental toxicity, based on the available data. Our conclusion is justified below.

Discussion and justification of our conclusion
Norway proposed a classification for 8:2 FTOH equal to PFOA using a weight-of –evidence approach based on the following arguments:
1) ADME consideration of female rats exposed to FTOH, and their low levels of serum metabolites, combined with:

2) supportive information concerning developmental effects of one major serum metabolite (PFOA),
3) the long half-life of PFOA in humans (2-4 years) and bioaccumulation, and
4) coherent developmental effects following exposure to 8:2 FTOH and PFOA,

Below our opinion on the 4 arguments are given.

1) ADME consideration
In female rats, serum levels of PFOA are very low compared to male rats as well as to female mice. This is due to the high elimination of PFOA in female rats. Therefore, Norway considered the rat a poor model to reveal potential developmental effects of 8:2 FTOH. The Netherlands do not fully agree with this reasoning. This is only correct for developmental effects due to the formation of PFOA. However, there is no information showing that the study in rats is not relevant for FTOH itself or the other metabolites.

2) metabolite PFOA
Norway provided information on the classification on PFOA in section 4.11.3 of the CLH report. The classification for PFOA was agreed by the TC C&L group in October 2006 for Repro. 1B, H360 D, based in read-across (agreed in RAC), but the substance is not yet included in Annex VI of CLP Regulation. APFO when dissolved in water will form the anion PFOA and the cat ion NH4+. Since the cat ion is identical to PFOA, read-across between APFO and FPOA regarding developmental properties is considered valid by the Netherlands. As a consequence, the Netherlands agree with the conclusion that PFOA has the potency to induce developmental effects.

3) half-life of PFOA
Norway concluded that PFOA have the ability to accumulate in humans. This conclusion is based on, among others, studies of Nilsson et al. (2010) and Fromme et al. (2009) The study of Nilsson et al. (2010) strongly suggests that human do metabolize 8:2 FTOH to PFOA resulting in internal exposure to PFOA after external exposure to 8:2 FTOH. PFOA has a long half-life in the human body (2-4 years) and there are indications that there is a risk of accumulation of PFOA in the human body during prolonged exposure. In the study of Fromme et al. (2009) mean serum concentrations of PFOA in the range of 500 to 7000 ng/ml depending on the type of job were measured in

fluorochemical production workers (Fromme et al., 2009). In professional ski waxers, the median concentration of PFOA was determined to be 50 ng/ml (15-174 ng/ml), stated to be 25 times higher than background levels.

The Netherlands agree with the conclusions that there is strong indication that 8:2 FTOH is metabolized to PFOA in the human body and that there is indication that PFOA can accumulate in the human body during prolonged exposure.

However, persistency and the potential for bioaccumulation of PFOA in the human body alone is no reason for classification for developmental toxicity. However, we agree that the higher accumulation in humans compared to rats and mice is an indication that the results in these species may not be predictive for humans.

4) Coherent developmental effects following exposure to 8:2 FTOH and PFOA
According to Norway, the findings in the developmental rat studies 8:2 FTOH are not of sufficient adversity to warrant classification. In a one generation study with 8:2 FTOH in rat (Mylchreest et al., 2005a), developmental effects were observed. The effects include reduced litter size at birth and reduced number of live pups per litter on day 0. The effects were observed at the NOAEL for maternal toxicity. This study was performed with a mixture of different FTOHs of which 27% was 8:2 FTOH. Therefore, it is unknown whether the developmental effects observed are induced by 8:2 FTOH or by the remaining 73% of other components.
The Netherlands is in agreement with this statement for rats.

However, for mice we do not agree that there are coherent developmental effects following exposure to 8:2 FTOH and PFOA.
The Netherlands wants to stress that the CLH report on 8:2 FTOH does not reveal whether the PFOA serum levels after 8:2 FTOH administration are high enough to induce developmental effects. We think that this information is essential to conclude on the need for classification of FTOH.

To be able to answer the question whether PFOA serum levels after 8:2 FTOH administration are high enough to induce developmental effects, toxicokinetic studies in which PFOA serum levels are measured after 8:2 FTOH administration should be compared with studies in which PFOA serum levels are measured after PFOA administration. In the CLH report, the mouse is considered the test animal of choice. Therefore, preferably information on serum levels derived from mouse studies after exposure to PFOA or FTOH should be compared. Two toxicokinetic studies with 8:2 FTOH in mice are mentioned in the proposal (Henderson et al. (2007) and Henderson and Smith (2007)). However, toxicokinetic studies with PFOA in mice are scarce. The EPA risk assessment of PFOA (2005) mentioned that there is limited information on the metabolism and pharmacokinetics of PFOA in mice. No toxicokinetic studies with mice were summarized by the EPA.

A search in the public literature revealed a study of Lau et al. (2006). In this study, adult male and female rats and mice received daily doses of PFOA of 10 mg/kg for 20 days and 20 mg/kg for 17 days, respectively. In this study, PFOA is dosed repeatedly, where in the studies of Henderson et al. (2007) and Henderson and Smith (2007) only a single dose was administered. Therefore, and because of the long estimated half-life of PFOA (15.6 days in males; 21.7 days in females), it is of no use to compare the PFOA serum levels after (repeated) dosing of PFOA with PFOA serum levels after (single) dosing of 8:2 FTOH.

Another study revealed in the public literature search is a study of Fenton et al (2009). In this study CD-1 mice received a single dose of PFOA by gavage of 5 mg/kg bw on gestation day 17. Serum levels on GD18 were about 8 000 ng/ml serum. A comparison of the results from this study with the results of the studies of Henderson et al. (2007) and Henderson and Smith (2007) indicate that a 8:2 FTOH dose of 6 times the dose of PFOA resulted in 1/8 of the PFOA serum level. We consider it useful to include this study in the CLH report and to make the comparison in PFOA serum levels after exposure to FTOH or PFOA.

The study of Fenton et al. indicates that PFOA serum levels after PFOA administration are far higher then after 8:2 FTOH administration. Thus, to reach similar PFOA serum levels, far higher administrated doses of 8:2 FTOH are needed compared to PFOA. Therefore, it cannot be excluded

that the relatively high levels of 8:2 FTOH induce maternal toxicity without reaching PFOA levels that are high enough to induce developmental toxicity. In this situation, there is no ground for classification of the substance for developmental toxicity. Since no developmental studies with mice after administration of 8:2 FTOH are available, it is not possible to conclude on the maternal toxicity occurring in mice due to the administration of 8:2 FTOH.

Conclusion
In summary, the developmental toxicity studies performed with rat do not trigger classification of 8:2 FTOH for developmental toxicity. However, we agree with Norway that rat is not the test animal of choice for studying the developmental effects of 8:2 FTOH. The toxicokinetic studies in mice indicate that PFOA serum levels after 8:2 FTOH administration are far lower than after PFOA administration. Because, it cannot be excluded that maternal toxicity occurs at lower concentrations than developmental toxicity, the observation that PFOA is formed after 8:2 FTOH administration alone is no trigger for classification for developmental toxicity.
The Netherlands agree with the conclusions that there is strong indication that 8:2 FTOH is metabolized to PFOA in the human body and that there is indication that PFOA can accumulate in the human body during prolonged exposure. However, persistency and the potential for bioaccumulation of PFOA in the human body alone is no reason for classification for developmental toxicity. There is no direct evidence that PFOA accumulation in humans due to metabolism after FTOH exposure can result in serum concentration high enough to induce developmental effects. The required FTOH exposure could be limited due to the toxicity of FTOH in humans.
As there is no direct evidence of developmental effects in humans or animals and the indirect evidence is limited, we do not agree with the proposed classification for developmental toxicity. Based on the available data we would propose no classification.

References
Lau C, Thibodeaux JR, Hanson RG, et al. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 2006;90(2):510-518

Fenton SE, Reiner JL, Nakayama SF, et al. 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. Reprod Toxicol 2009;27(3-4):365–372

Dossier Submitter's Response

Thank you for your comments.

1) The findings of the developmental studies 8:2 FTOH are not considered of sufficient adversity to warrant classification, even if referred studies report qualitatively similar findings. As part of a weight-of-evidence approach, we consider the rat as a poor model to reveal potential developmental effects of 8:2 FTOH and its metabolites, especially the female rat, due to ADME considerations.
2) Noted
3) Noted
4) See response to comments from Sweden (comment no. 9)

RAC opinion

The view of RAC on the data is quite similar to the view expressed by the Netherlands, and the classification proposal is hence not supported by the RAC.

Date	Country	Organisation	Type of Organisation	Comment number
25/05/2012	Germany		MSCA	6

Comment received

Chapter 4.11.6 of the dossier summarises the rationale for a developmental toxicity classification of FTOH:

"Using a weight-of–evidence approach based on

1) ADME consideration of female rats exposed to FTOH, and their low levels of serum metabolites combined with

2) supportive information concerning developmental effects of one major serum metabolite (PFOA),

3) the long half-life of PFOA in humans (2-4 years) and bioaccumulation and

4) coherent developmental effects following exposure to 8:2 FTOH and PFOA, we propose a classification for 8:2 FTOH equal to PFOA."

For the following reasons this rationale is not sufficiently convincing as justification for classification for developmental toxicity of FTOH:

Item 4 might be misleading. Both FTOH and APFO (not PFOA) were experimentally tested for developmental toxicity. There are only rat data available for FTOH, while for APFO both rat and mouse developmental toxicity data are available. The first developmental study (Mylchrest et al., 2005b) was performed with pure FTOH. Maternal toxicity was observed in the highest dose group only. The main effect was delayed skull bone ossification starting (in foetuses (and litters)) with 22(8) in the control group, 31(12) in the low dose group and 45(16) in the middle dose group. Values of the highest doses group (55(12)) should be considered with care since maternal toxicity was observed. The results show a clear dose-dependent increase in delayed ossification. In an independent study (Mylchrest et al., 2005a) the treatment with a FTOH containing mixtures yielded in reduced litter sizes at birth (from 100 mg/kg bw/day) and number of live pups per litter on day 0. No maternal toxicity was observed at the dose. However, a clear dose response relationship is missing for the highest dose.
The APFO mouse developmental toxicity data justify the developmental toxicity classification for APFO. Thus the Dossier submitter's statement of "coherent developmental effects following exposure to FTOH and PFOA" is misleading, because FTOH was not tested in the experimental test system (mice) that resulted in those developmental toxicity findings that triggered developmental toxicity classification for APFO (early full litter resorptions and perinatal pup viability). Thus, we do not recognise coherent developmental toxicity effects in both substances because the missing mouse data for FTOH do not allow for this comparison.

With respect to item 1 and item 4: The experimental developmental toxicity data for FTOH alone do not allow a firm conclusion on FTOH; with the consequence that the classification for FTOH needs to be mainly related to the information that APFO/PFOA is a metabolite of FTOH (see item 2 of the dossier submitter's justification).

With reference to item 3: we consider the relative half-lifes of PFOA in rats, mice and humans as findings to be accounted for classification purposes. But we think, that a relatively long half-life in humans is not to be considered a sufficient justification for a dev tox classification of FTOH (or APFO). The main reasoning for a FTOH dev tox classification in our opinion should be either positive findings in FTOH dev tox testing in mice. The assumption can not be excluded, that the rate of metabolism of FTOH to APFO/PFOA in rodents and humans is sufficiently high in order to trigger the APFO dev tox findings. This analysis we do not really find in the CLH report: we propose to consider this aspect and to compare the effective PFOA blood levels following oral exposure of APFO in the dev tox mice studies with those PFOA blood levels that could be achieved in oral testing of FTOH in rodents. And finally, we suggest the presentation of supporting human data on the metabolism of FTOH to PFOA, if available. This sort of analysis should of course be complemented by a comparison of PFOA toxicokinetics in mice and humans.

Minor editorial comments: On page 22, third paragraph: "After 6h following 30 mg 8:2 FTOH/kg bw, 972 mg PFOA/ml serum was measured (Henderson et al., 2007)". The reference Henderson et al., 2007 is not mentioned in the reference list, only Henderson & Smith, 2007 has been referenced. It is very likely, that the missing reference is Henderson WM, Weber EJ, Duirk SE, Washington JW, Smith MA (2007) Quantification of fluorotelomer-based chemicals in mammalian matrices by monitoring perfluoroalkyl chain fragments with GC/MS. J Chromatogr B Analyt Technol Biomed Life Sci.;846:155-161.
When checking the reference Henderson & Smith, 2007, the values in mouse plasma amounted to

several hundred ng PFOA/ml.

Dossier Submitter's Response

Thank you for your comments.

Noted.

For item 4) it could be specified that the studies on 8:2 FTOH are in rat and the studies on PFOA are in both rat and mice.

For item 3) see response to comments from Sweden (comment no. 9).

The information mentioned on page 22 of the CLH Report 2012, paragraph 3, i.e. *"… in male mice (…) 972 mg PFOA/ml serum…"*, the unit should be *"… 972* ***ng*** *PFOA/ ml serum…".*The missing reference should be Henderson WM, Weber EJ, Duirk SE, Washington JW, Smith MA (2007) Quantification of fluorotelomer-based chemicals in mammalian matrices by monitoring perfluoroalkyl chain fragments with GC/MS. J Chromatogr B Analyt Technol Biomed Life Sci.;846:155-161.

RAC opinion

The view of RAC on the data is quite similar to the view expressed by Germany, and the classification proposal is hence not supported by the RAC.

Date	Country	Organisation	Type of Organisation	Comment number
31/05/2012	Belgium		MSCA	7

Comment received

Belgium thanks the dossier submitter for the clear well-documented proposal for 8:2 Fluorotelomer alcohol.

We are in favour of the proposal for classification Rep. 1B H360D.

We agree to consider the rat as a poor model to reveal potential developmental effects of 8:2 FTOH due to its rapid/complete clearance, including its metabolites, from the tissues. As PFOA is one major urine metabolite following exposure to 8:2 FTOH, we support the weight-of-evidence approach based on the supportive information concerning developmental effects of PFOA.

Effects via lactation
We would like to request the DS further information regarding the effects via Lactation. PFOA has been classified based on clear evidence on developmental effects from perinatal studies in mice exposed to APFO. Besides, there is sufficient evidence from mouse studies with postnatal administration of APFO that indicated adverse effects (delayed/stunted mammary gland development in the offspring) which cause concern for the health of a breastfed child. An additional classification on lactaction effects has been agreed.

In the proposal, it is mentioned that PFOA was found to be excreted into milk after oral exposure to 8:2 FTOH in pregnant mice. In rats, the findings of the one generation study indicate a reduction of the number of live pups per litter on lactation day4.

Regarding this information stated in the proposal, we request information on the relevance of possible effects of 8:2 FTOH via lactation.

Dossier Submitter's Response

Thank you for the support.

The proposal was submitted before RAC concluded on the classification for PFOA. We encourage RAC to consider the relevance of possible effects via lactation also for 8:2 FTOH.

RAC opinion

The RAC is of the opinion that there is, at present, not sufficient metabolic information to support that PFOA is a major metabolite likely to exert reproductive toxicity after exposure to 8:2 FTOH. The classification proposal is hence not supported. By that follows that classification for effects via lactation is not considered relevant by the RAC.

Date	Country	Organisation	Type of Organisation	Comment number
31/05/2012	United Kingdom	HSE UKCA	MSCA	8

Comment received

Summary and discussion of reproductive toxicity. We note that RAC agreed a classification for Effects on or via Lactation for PFOA and APFO because of delayed/stunted mammary gland development in mice that had been exposed to APFO via the milk. We also note that toxicokinetic data in mice demonstrated that PFOA is transferred to pups during lactation on dams that are dosed with 8:2 FTOH (Henderson and Smith, 2007). Although this end-point is not harmonised in accordance with CLP Article 36 (1)(d), we suggest that it should be considered in the dossier.

Dossier Submitter's Response

Thank you for the comments. See response to comments from Belgium (comment no. 7).

RAC opinion

The RAC is of the opinion that there is, at present, not sufficient metabolic information to support that PFOA is a major metabolite likely to exert reproductive toxicity after exposure to 8:2 FTOH. The classification proposal is hence not supported. By that follows that classification for effects via lactation is not considered relevant by the RAC.

Date	Country	Organisation	Type of Organisation	Comment number
01/06/2012	Sweden		MSCA	9

Comment received

8:2 FTOH is metabolized to PFOA which will soon be classified in category 1B for reproductive toxicity (developmental). The dossier submitter for FTOH proposes a classification equal to that of PFOA (repro 1B) because of the following:
1) FTOH is metabolized into PFOA, and PFOA is already classified in category 1B for reproductive toxicity.

2) PFOA has a very long half-life in humans and bioaccumulation is highly plausible.
3) Developmental toxicity has been seen in animal models after exposure to PFOA.

In toxicokinetic animal- and in vitro studies; FTOH is metabolized to some extent into PFOA. In an in vitro study by Nabb et al. (2007), PFOA was generated from FTOH in hepatocytes. The percentage of conversion to PFOA was 0.47; 0.24 and 0.02% in mouse, rat and human hepatocytes respectively. Humans seem to form much less PFOA from FTOH than rodents (negligible amount?) No other data on human FTOH-metabolism are presented in the dossier.
On the other hand, the half-life of PFOA in humans is 2-4 years compared to hours/days in rodents. This could potentially cause significant bioaccumulation of PFOA in humans exposed to FTOH, even if only a very small fraction of the FTOH is metabolized into PFOA.
The dossier presents three studies assessing reproductive toxicity where rats were exposed to FTOH. The study results indicate that FTOH exposure might cause developmental effects but the effects are not sufficiently adverse to warrant classification on their own.
A number of epidemiological studies of ski waxers etc. are presented where the ability of PFOA to bioaccumulate in humans is demonstrated. However, it is not clear exactly to which compounds the study participants have been exposed, it appears to be a blend containing bothFTOH and PFOA as well as other similar chemicals in uncertain ratios. Therefore it is impossible to draw any conclusion about human metabolism of FTOH from these studies; all they show is that the human body bioaccumulates PFOA when exposed directly or indirectly (via metabolism) to the compound.
The following calculation roughly estimates how much FTOH a person would need to ingest to form sufficient levels of PFOA to cause negative effects on reproduction. The threshold dose for PFOA to cause developmental effects in rodents is roughly around a couple of mg/kg. Using the only information available on human metabolism of FTOH (i.e. 0.02% conversion to PFOA in human hepatocytes); a person weighing 70 kg would need to ingest a whole 700 grams of FTOH to produce a concentration of 2 mg/kg PFOA in their body. Is it reasonable that a person would ingest 700 grams of FTOH, even if the exposure is spread out over the person's lifetime?
In addition, the 0.02% conversion rate to PFOA can also be compared to the 0.3% concentration limit that applies as default to reproductive toxicants in category 1B. FTOH could be seen as

indirectly containing 0.02% PFOA which is still well under the concentration limit for classification.
Taken together, this classification proposal is a borderline case where some evidence has been provided that FTOH could potentially cause developmental toxicity. However, important data is lacking and more information on the toxicokinetics of FTOH needs to be presented before it can be justified to place 8:2 FTOH in category 1B for reproductive toxicity.

Dossier Submitter's Response

Thank you for the comments.

Although the biotransformation of 8:2 FTOH to PFOA in humans seems to be low, the half-life of PFOA in humans is very long ($T_{1/2}$ of 3.8 years), and humans have a significantly slower elimination rate than rodents (from hours to days in rats and mice respectively). Based on human studies, PFOA accumulates with time and exposure. Taken together, a classification based on PFOA should be considered for developmental effects of 8:2 FTOH.

It is important to keep in mind that this is not a risk assessment. For classification only intrinsic properties should be taken into consideration.

However, it could be considered if setting of a higher specific concentration limit for FTOH could be relevant because of the indirect exposure to PFOA.

RAC opinion

The RAC is of the opinion that there is, at present, not sufficient metabolic information to support that PFOA is a major metabolite likely to exert reproductive toxicity after exposure to 8:2 FTOH. The classification proposal is hence not supported.

Date	Country	Organisation	Type of Organisation	Comment number
01/06/2012	Switzerland	DuPont de Nemours International Sàrl	Company-Manufacturer	10

Comment received

Clariant and DuPont strongly disagree with the Norwegian Climate and Pollution Agency's proposal to classify 8:2 FTOH for developmental toxicity. A detailed assessment and a cover letter can be found in the attached archived zip file entitled 20120601_Norway_CLHComments.zip

ECHA comment: The document: [20120601_Norway_CLHComments.zip] was submitted as a separate attachment. Attachment no. 1. The cover letter (20120601_Cover letter.pdf) is copied below:

Dear Members of the Risk Assessment Committee,

We kindly submit for consideration by the Risk Assessment Committee (RAC) the enclosed comments on the most recent Annex XV Harmonized Classification & Labeling (CLH) report for the chemical 8:2 Fluorotelomer Alcohol (8:2 FTOH, CAS number 678-39-7, EC number 211-648-0) prepared by the Norwegian Climate and Pollution Agency, and posted on ECHA's website for public consultation on April 17, 2012.

As pointed out in our first document dated September 9, 2010, there is sufficient 8:2 FTOH hazard data available to make a classification and labeling assessment according to published EC criteria. The proposed developmental toxicity classification (Repr. 1B - CLP criteria) proposed by the Norwegian Climat and Pollution Agency (20 March 2012) relies on a read across strategy to the minor metabolite PFOA which is in our opinion scientifically neither warranted nor justified.

Consequently, as stated in our 2010 comments, we propose 'no hazard or environmental classification' of 8:2 FTOH.

We do hope you will find the information presented in the aforementioned document useful in your assessment for a harmonized classification and labelling of 8:2 FTOH. Please do not hesitate to contact us should there be any questions regarding our proposal.

With kind regards,

Dossier Submitter's Response

Thank you for your comments.

We have commented on ***your main points and detailed arguments*** which are reproduced below in bold italics.

Main points:

There is sufficient developmental toxicology study data for 8:2 FTOH and other relevant information to assess hazard classification. These data support no classification.

The findings of the developmental studies with 8:2 FTOH are not considered sufficient to warrant classification. In addition, we consider the rat a poor model to reveal potential developmental effects of 8:2 FTOH and its metabolites, especially the female rat, because they seem to have a lower biotransformation of 8:2 FTOH to PFOA than males. Therefore we have focused on the mice studies on PFOA which is an important metabolite in the degradation of FTOH. See CLH report for more details concerning mouse as a better model.

Read-across to PFOA, a minor metabolite of 8:2 FTOH metabolism by both the oral and inhalation exposure routes, is not appropriate with respect to an assessment on hazard classification on 8:2 FTOH. The toxicological profile of 8:2 FTOH is not identical to or dominated by the minor metabolite PFOA. 8:2 FTOH and PFOA are very different chemically and biologically.

See response to this comment below.

The CLH Proposal by Norway fails to meet the weight-of-evidence and read-across scientific criteria set out by both ECHA and OECD required to substantiate read across from PFOA to 8:2 FTOH.

Our CLH proposal is based on a weight-of-evidence determination according to CLP Annex I, 1.1.1 and not on read-across. Hence the stepwise approach described in ECHA/OECD guidances on category approach is not warranted.

This is also in line with the Guidance on information requirements and chemical safety assessment - R.7A Endpoint Specific Guidance, Introduction which states that 'In the context of evaluating

substances for their effects, it is important to note that when they are released into the environment or taken up by animals, they may be transformed through degradation or metabolism. These processes and their outcome may need to be taken into account in the overall assessment.'

Detailed comparison of kinetics of parent compound 8:2 FTOH and metabolites in rat vs. mouse vs. human, including new literature references, do not support hazard classification for developmental toxicity.

We disagree. We consider mouse as the most appropriate model. See CLH report for more details.

Published peer-reviewed data rejects the idea of PFOA accumulation with age.
One explanation for the statement "PFOA serum levels in the general population have been reported not to significantly increase with age" could be that children have increased exposure compared to adults; eg. from contact with carpeted floors and upholstered furniture coupled with hand-to-mouth activity. Carpets and upholstered furniture are known to trap dust, which may contain perfluorinated compounds. Adults today were not exposed to the same levels of perfluorinated compounds in childhood.

Detailed arguments:
In the section 4.11.5 "Comparison with criteria" of the CLH Report 2012 it is stated that: "The findings of the developmental studies 8:2 FTOH are not considered of sufficient adversity to warrant classification… " however, further down: " …the findings in the developmental studies (Mylchreest et al ., 2005 a and b) suggest the occurrence of similar developmental effects on offspring as following exposure to PFOA."…
Industry disagrees with the assessment that the developmental studies may indicate effects similar to PFOA based on the following points:
a) None of the 2 developmental toxicity studies referenced report on adverse findings which warrant a classification for developmental toxicity. No malformations were reported and minor alterations are not subject to reprotox hazard classification. Even more, the CLH Report 2012 itself summarized that "the findings of the developmental studies 8:2 FTOH are not considered of sufficient adversity to warrant classification, even if referred studies report qualitatively similar findings". A "suggestion that the observations from these studies can be directly linked to adverse effects "following exposure to PFOA" is speculation and not justified.

We agree that the effects in the studies are not coherent, but we consider that there is some similarity in the developmental effects following exposure to 8:2 FTOH and PFOA.

Besides the general limitation of the study as being performed with a mixture, the authors themselves concluded from their study that ."no developmental effects were observed at dose levels that did not adversely affect adult animals". In addition, the findings of reduced litter size at 100 and 250 mg/kg bw are difficult to assess in terms of relevance for classification. The findings may be spurious and cannot clearly be related to treatment of fluorotelomer FTOHs since the data are confounded for two reasons: 1) the observance of findings in only 2-3 litters and not across the whole treatment group and 2) as reported in the publication (Mylchreest et al., 2005a), the reduced litter size observed was not due to death in utero but rather to cannibalization of neonates shortly after death with no additional deaths after PND 4.

One possible explanation for cannibalization is that the dam is eating not viable neonates with developmental effects.

PFOA is a minor metabolite.

We agree that PFOA is a minor metabolite. However it is among the principal metabolites in urine according to Fasano et al. 2009:
Most radioactive 8:2 FTOH was found in the faeces (mice were not bile duct cannulated), relatively more at the higher dose. Elimination via urine was minor (2.48-8.98% of recovered dose), with females eliminating more than males (2-3 times). The principal metabolites in urine were

PFOA(range: 0,06-1,76%), 7-2 sFTOH-gluc (females only, range: 0,72-0,78%) and 8-2 uFTOH-SCysNAcetyl (females only, range: 0,17-0,55%).

8:2 FTOH is a significant peroxisomal proliferator in mice (Kudo et al., 2005), as Peroxisomal acyl-CoA oxidase activity was increased 6-fold after repeated exposure of 50 (0.025%) or 100 (0.05%) 8:2 FTOH mg/kg bw in mice. This effect was accompanied by a 45-80% increase in liver weight. The observation that peroxisomal proliferators can induce effects on post-natal body weight gain and survival that are not seen in knock out mice (Abbott et al., 2007), calls into question the appropriateness of wild-strain mice as a superior system for assessing developmental toxicity to humans.
In addition, the sensitivity of the mouse liver to fluorotelomer alcohol makes it infeasible to evaluate developmental toxicity independent of liver toxicity. Significant liver weight increase by PPARα and enzyme induction has been observed after single and repeated exposure to 8:2 FTOH at doses of 50-100 mg/kg bw in mice (see discussion of Kudo et al., 2005, above). Such changes can disturb homeostasis in pregnant mice even without significant effects on body weight during development.
These doses of 8:2 FTOH would not be considered appropriate for a mouse developmental toxicity study, as it would be difficult to interpret the developmental effects in mouse in the presence of confounding effects of the PPARα response and concomitant liver effects.

Both mice and rats are more sensitive to peroxisom proliferators than humans. Hence, these issues will also apply to rats. See Annex 1 for a further discussion.

From a pharmacokinetic standpoint, the conversion rate of 8:2 FTOH to PFOA supports the mouse as most sensitive rodent model for assessment of PFOA-mediated toxicity after administration of 8:2 FTOH. However, it is clear that the mouse is not more closely related to humans based on a comparison of the in vitro rates of conversion from the Nabb et al., 2007 experiments. The rates were calculated for whole-body conversion to be 54.9, 23.4, and 2.47 nmol/h/kg bw for mice, rats, and humans, respectively (see supplementary data from Nabb et al., 2007 for calculations). This indicates a 22-fold ratio of PFOA conversion in mouse vs. human, compared to a 9.5-fold ratio for rat vs. human. This suggests the rat as an adequate, and possibly more appropriate, animal model for comparison to humans.

Although the biotransformation of 8:2 FTOH to PFOA in humans seems to be low, the half-life of PFOA in humans is very long. Based on human studies PFOA accumulates with time and age. Like humans mice get higher levels of PFOA after 8:2 FTOH administration than rats and is therefore a better model.

Haug et al. (2009) in a study titled "Time Trends and the Influence of Age and Gender on Serum Concentrations of Perfluorinated Compounds in Archived Human Samples" (Environ. Sci. Technol. 2009, 43, pp. 2131–2136) concluded: For several so-called legacy persistent organic pollutants, e.g., polychlorinated biphenyls (PCBs), the concentrations in human serum increases with age and the concentrations are higher in males than females. But for the PFCs, the results seem to be more varying. This difference may be explained by the fact that PCBs are lipophilic and accumulate with time in the lipid stores of the body, while the PFCs are protein bound and not stored in lipids. Thus, a strong association between PFCs (including PFOA) and age is not expected.

Two recent publications (Haug et al., 2010; Haug et al., 2011) cited in the Norwegian CLH Report 2012 (pages 25-26) clearly contradict the assertion in the report as stated in the author's own words. Quoting from Haug et al., 2011: "no significant relationship between the total PFOA intakes and the corresponding serum concentrations were seen". In addition, the authors state, "In contradiction to what was observed in our previous study (Haug et al., 2010), no significant relationship between dietary intake and concentrations of PFOA in serum were observed".

One explanation for the statement "PFOA serum levels in the general population have been reported not to significantly increase with age" could be that children have increased exposure compared to adults; eg. from contact with carpeted floors and upholstered furniture coupled with hand-to-mouth

activity. Carpets and upholstered furniture are known to trap dust, which may contain perfluorinated compounds. Adults today were not exposed to the same levels of perfluorinated compounds in childhood.

The CLH draft report states that "a threshold is considered to exist for a potential carcinogenic effect for PFOA and that possibly relatively low levels of PFOA is metabolized from 8:2 FTOH in humans, a classification for carcinogenicity is not further considered. Only a classification for reproductive toxicity for 8:2 FTOH is proposed" (pages 56, paragraph 1). The threshold consideration is valid for the reprotoxicity evaluation as well. Since it is generally accepted that effects on reprotoxicity have a clear threshold the threshold argument presented for potential carcinogenic effect equally applies and should be considered for the reprotoxicity endpoint as well (CLH Report 2012, p. 56, paragraph 1). The same low levels of the minor metabolite PFOA exist independent of the toxicological endpoint. Therefore, as applied to one endpoint, carcinogenic effect, with the conclusion of no classification it is valid to argue that such an interpretation should be applied against a reprotoxicity classification as well. The existence of a threshold is clearly supported by the EFSA in the published value of a tolerated daily intake for PFOA (EFSA, 2008).

We agree that the threshold consideration is relevant for addressing both hazard categories, and based on the outcome of the RAC opinion we might reconsider the carcinogenicity of 8:2 FTOH.

In a follow up study by Nilsson et al 2010 the objective was to determine concentrations of PFCAs, PFSAs and FTOHs in air collected in the respiratory zone of ski wax technicians' during work. The results show daily inhalation exposure of 8:2 FTOH (range = 830-250000 ng/m^3) in air which is 800 times higher than levels of PFOA (range = 80-4900 ng/m^3) in air. This suggests internal exposure of PFOA through biotransformation of 8:2 FTOH to PFOA and PFNA in humans (Nilsson et al 2010b).

PFOA is confirmed as a metabolite of 8:2 FTOH. When exposed to high levels of 8:2 FTOH it is very likely that some of the PFOA in the blood is metabolized from 8:2 FTOH.

- For mistakes see response to comment no. 2 and 6.
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RAC opinion

The RAC notes that there is only one study on 8:2 FTOH, and agree with that study is not supporting C&L. The approach chosen is not a 'read across' in the sense of the OECD guidance document, but rather using data from a common significant metabolite. However, it is not shown by the DS that the formation of PFOA is sufficient for classification. The approach as such is, however, very much in line with the guidance and is accepted by the RAC. We agree that accumulation of PFOA with age is not proven in the dossier. The RAC agree with the view that no classification for reproductive toxicity is warranted for 8:2 FTOH based on the present database.

Date	Country	Organisation	Type of Organisation	Comment number
01/06/2012	United States	FluoroCouncil	Industry or trade association	11

Comment received

As detailed in the attached comments, the listed members of the FluoroCouncil believe the classification for 8:2 FTOH proposed in Norway's CLH report should be rejected on the grounds that read across to PFOA is not warranted and/or justified. Norway's proposal to classify 8:2 FTOH as a Reprotoxicant Category 1B (CLP Regulation) is mainly based on the argument that PFOA is a major metabolite of 8:2 FTOH. This is in clear contradiction with published scientific data. Consequently, PFOA being only a minor metabolite of 8:2 FTOH, read across cannot be applied as it is not in accordance with the read across justifications as stated in EU-adopted official technical guidance documents.

ECHA comment:The document (FC FTOH Comments FINAL 2012-0531.pdf) was submitted as a separate attachment. Attachment no. 2.
Dossier Submitter's Response
Thank you for your comments. See response to comments from DuPont (comment no. 10).
RAC opinion
The approach chosen is not a 'read across' in the sense of e.g. the OECD guidance document, but rather using data from a common significant metabolite. However, it is not shown in the present dossier that the formation of PFOA is sufficient for classification. The approach as such is, however, very much in line with the guidance and is accepted by the RAC.

RESPIRATORY SENSITISATION - no comments received

OTHER HAZARDS AND ENDPOINTS - - no comments received

REFERENCES: None

ATTACHMENTS RECEIVED:

1. **20120601_Norway_CLHComments.zip** consists of 2 files:
   - 20120601_Cover letter.pdf, part of the document is copied in the table.
   - 20120601_Comments_NorwayCLH.pdf

   Comment no. 10, submitted by Switzerland/ DuPont de Nemours International Sàrl / Company-Manufacturer on 01 June 2012.

2. **FC FTOH Comments FINAL 2012-0531.pdf** (FluoroCouncil Comments on the Norwegian Proposed Classification (March 2012) of 8:2 FTOH for Developmental Toxicity). Comment no. 11, submitted by United States / FluoroCouncil / Industry or trade association on 01 June 2012.