Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol

EC Number: 211-477-1
CAS Number: 647-42-7

CLH-O-0000007052-84-01/F

Adopted

26 November 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3,3,4,4,5,5,6,6,7,7,8,8,8-TRIDECAFLUOROOCTAN-1-OL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol
EC number: 211-477-1
CAS number: 647-42-7
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2021	Belgium	Chemours Netherlands BV, for Fluorotelomers REACH consortium	Company-Importer	1
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment 6-2 FTOH CLH response 08-Apr-21.pdf				
Dossier Submitter's Response				
Thank you for your support on the classification proposal and for your indications from the draft results of the OECD TG 234 study. As the results of the OECD TG 234 study are not available at the time point of evaluation and derivation of the harmonised classification, the DS could not consider them. RAC may decide over the harmonised classification having regard to the results of the OECD TG 234 study.				
RAC's response				
Thank you for the OECD TG 234 study. RAC takes note of the additional information provided.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2021	Sweden		MemberState	2

Comment received

STOT RE 2
We support the proposed classification STOT RE 2. As presented in the CLH-proposal, a recurring target is the teeth, described in four oral studies and one inhalation study. The effects observed indicative of dental fluorosis (e.g. discolored teeth, broken/missing incisors, degeneration of ameloblastic epithelium, and decalcification of enamel and/or dentin), likely caused by the defluorination of 6:2 FTOH leading to the observed increase in plasma fluoride levels, are effects of relevance to humans and should be considered adverse. The category 2 classification seem appropriate based on a weight of evidence approach. Although the effects at 25 mg/kg/d in the 28d oral study could result in a category 1 classification, when extrapolating using Haber's law, the other longer-term studies suggest that the effects on teeth occur at dose levels between 25 to 100/125 mg/kg/d and are more in line with a category 2 classification.
Increased plasma fluoride levels in humans may lead to dental as well as skeletal fluorosis. In the studies evaluated in this proposal, dental fluorosis was shown, however no effects on bone were described, other than an incomplete decalcification of nasal bones in mice at 100 mg/kg/d, due to lack of evaluation of bone in the studies. Effects on bone may have occurred in the animals, but any such effect has not been substantiated in the studies. Whether the increased plasma fluoride levels and dental fluorosis, together with the effect on nasal bones in mice, are sufficient as surrogate for effects overall on bone is borderline. If not, a STOT RE 2 (teeth) classification should be appropriate.
One other target organ that has not been discussed in the proposal for STOT RE classification is the liver. The liver is a common target organ for perfluoroalkylated acids, such as the perfluorinated carboxylic acids PFOA and PFHpA. Effects on the liver were observed in most of the studies evaluated in this proposal, including increased liver weight, histological effects and increases in clinical markers (AST/ALT/ALP) indicative of liver toxicity. In the combined repeated-dose and reproductive toxicity study in mice (Mukerji et al., 2015), where females and males were orally exposed to 6:2 FTOH for 67 and 84 days, respectively, significantly increased liver weights were observed at 100 mg/kg/d together with hepatocellular single cell necrosis in 12/15 animals of both sexes and significantly increased levels of AST, ALT and ALP, all indicative of liver toxicity. One of the metabolites of 6:2 FTOH, PFHpA, was recently classified as STOT RE 1 for liver toxicity based on increased liver weight, hepatocellular single cell necrosis and significantly increased clinical markers of liver toxicity (ALP, ALT) in the mouse (ECHA, 2021). We therefore think that also liver toxicity should be considered for a possible STOT RE 2 classification in this proposal. The mouse has been considered a more suitable species for testing of perfluoroalkylated acids due to less rapid excretion in this species than in the rat.

Reference:
ECHA (2021). RAC Opinion proposing harmonised classification and labelling at EU level of Perfluoroheptanoic acid; tridecafluoroheptanoic acid.
https://echa.europa.eu/documents/10162/a51f690e-7865-9476-c9b2-a7144073af72

Dossier Submitter's Response

In our view, fluorosis should be considered as a systemic adverse effect affecting the whole skeletal system (bones and teeth). Mottled teeth are considered as an indicator for

the systemic disorder of bone metabolism, therefore an indication of the skeletal system primary target organ (system) is preferred. Alternatively, your proposal to indicate teeth as primary target tissue is also an option; however, an indication of teeth alone may lead to an underestimation of the importance for the entire skeletal system.

Although bone tissue was not regularly examined in all studies, two studies indicated that bone tissue is affected. Incomplete decalcification of bone tissue (in the nasal bone in Mukerji et al, 2015, in tibia and femur in DuPont, 2011) was observed as a consequence of fluoride-associated resistance to the acid decalcification procedure (in order to produce tissue sections for microscopy). Mukerji et al. interpretation of the effect as non-adverse is not supported by the DS as biomechanical properties (leading to increased fracture rates in humans) and bone morphology have not been assessed.

With regards to the proposal to include the liver as a second primary target organ, the following table presents the evidence for liver toxicity and resulting hazard class (based on Table 10 of the CLH Dossier, extended for liver effects):

Study reference	**Effective dose (mg/kg bw/d)**	**Length of exposure**	**Calculated d effective dose when extrapolated to 90-day exposure (according to 1272/2008, annex I, No. 3.9.2.9.5**	**Classification supported by the study**
Hita Laboratory (2007)	25 125	28 days	8 41	Effects on teeth: STOT RE 1 (≤ 10 mg/kg bw/d guidance value) Effects on the liver*: STOT RE 2 (≤ 100 mg/kg bw/d guidance value) In the absence of effects on the body weight, 125 mg/kg liver weight abs/rel (rel persistent after recovery) 25 mg/kg (f only), 125 mg/kg (m/f) liver enlargement 125 mg/kg (m/f) periportal/diffuse liver cell hypertrophy 125 mg/kg ALT (m) and GT (m/f) and total cholesterol (f) activity sign increased
Serex et al. (2014)	125	90 days	125	Effects on teeth: None (≤ 100 mg/kg bw/d guidance value) (Note: Elevated urine fluoride

				concentration ≥ 25 mg/kg bw/d in male rats, increased plasma fluoride, ≥ 25 mg/kg bw/d) Effects on the liver: None (relevant effect at significant potency only above guidance value) ≥25 mg/kg (m)and ≥125 mg/kg (f) rel. liver weight increased, not reversible at 1 mo recovery, but after 3 mo recovery ≥25 mg/kg (f) ≥125 mg/kg (m) single cell necrosis, vacuolisation, oval/biliary hyperplasia, hepatocellular hypertrophy and periportal inflammation, minimal at 25 mg/kg, reversible in m after 1 mo, most effects reversible in f after 1 mo, ≥125 mg/kg (f) after 3 mo biliary hyperplasia (non-reversible)
O'Connor et al. (2014)	125	At least 84 days	117	None (≤ 100 mg/kg bw/d guidance value) (design of the reproductive and developmental studies not suitable to assess liver toxicity)
Mukerji et al. (2015)	100	At least 84 days in males At least 67 days in females	93.3 74.4	Effects on teeth: STOT RE 2 (≤ 100 mg/kg bw/d guidance value) Effects on the liver: STOT RE 2 (≤ 100 mg/kg bw/d guidance value) 100 mg/kg (m/f) increased rel liver weight 100 mg/kg (m/f) increased levels of AST, ALT, ALP, SDH, total bile acids and (f only) total bilirubin 100 mg/kg liver toxic effects at 100, low incidence at 25 mg (hypertrophy, oval cell hypertrophy/hyperplasia, single cell necrosis, cystic

				degeneration ≥5 mg/kg hepatocellular hypertrophy (9-15 of 15 test animals/group), minimal at 5 and 25 mg/kg (m) and at 25 mgkg (f)

*The study of Hita Laboratory (2007) was said to be equivalent to the OECD TG 407. Some limitations as reduced list of organs (incisor, glandular stomach and liver only examined) investigated by microscopy were noted in the mid and low dose groups.

Adverse effects on the liver such as liver cell necrosis, (non-reversible) oval cell hyperplasia and elevated enzyme activities indicative of liver cell dysfunction/cytotoxicity and elevated/disordered bilirubin exretion were identified at the same dose or at a higher dose as effects on the teeth. Where liver effects were observed at lower doses than those inducing teeth abnormalities, their severity grade/potency was reported as minimal. Where hepatocellular hypertrophy occurs alone (if not accompanied by degenerative/inflammatory effects), this would not justify classification. In conclusion, the first organ system proposed to be mentioned remains the skeletal system (alternatively the teeth), liver effects are supportive for the proposed classification and could be added as a second primary organ system.

The proposal for STOT RE 2 for 6:2 FTOH is considered consistent with the classification of perfluoroheptanoic acid. Both substances are liver toxicants, in comparison it is noted that liver effects of perfluoroheptanoic acid started at lower doses and the database on severity grades across all dose groups/studies was better than for 6:2 FTOH.

RAC's response

RAC agrees with the classification STOT RE 2 for effects on teeth and bone. However, RAC does not agree with the DS proposal to specify 'skeletal system' as the target organ as it considers that the more severe effects on teeth should be clearly communicated, which is not the case if the broader term 'skeletal system' is used. Therefore, RAC proposes to specify 'teeth' and 'bone' as target organs.
Due to lack of quantitative details on the liver histopathological effects observed in the 90-day study in rats and in the 1-gen study in mice, RAC proposes no classification for liver effects.

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2021	France		MemberState	3

Comment received

Page 18: Please give a more substantiated explanation for the choice of category 2 and not category 1 than simply mentioning a weight of evidence approach. Particularly, you did not discuss/try to explain the discordance in results between the 28d and 90d studies: doses, species, and exposure were similar (such as quality of the studies according to your assessment), and effects on teeth occurs at a lower exposure level in the subacute study. Considering this, if no explanation can be proposed, and in a conservative approach, should a classification as STOT RE 1 considered?

Dossier Submitter's Response
Based on the effective doses demonstrated in Table 10 of the CLH dossier it is obvious that the only study supporting STOT RE 1 is the 28 day-study. Three studies with longer administration (of or around 90 days) demonstrated teeth abnormalities that either support STOT RE 2 or no classification. The study of Mukerji et al. (2015) supporting STOT RE 2 did not report teeth findings at 25 mg/kg bw/d and below. Taking the differences in the treatment duration into account, the lack of effects at 25 mg/kg bw/d is not consistent with the evidence seen at 25 mg/kg bw/d in the 28-day study (corresponding to 8 mg/kg bw/day in a 90-day design). If more weight is given on studies with longer duration, the outcome of the 90-day studies would justify STOT RE 2. If more weight is given on the most sensitive effect, the outcome could - based on the 28-day study - justify STOT RE 1. While weighing the arguments, it has also to be considered that the predominant findings in teeth were mainly identified as gross pathological findings (discolouration, mottled/broken/missing/misaligned teeth, surface delamination). Teeth were microscopically examined on decalcified H&E stained paraffin sections in some studies, but not all. In order to fully assess the detailed structures of mineralised and cellular components of teeth and the bone matrix, specific embedding techniques on decalcified and non-decalcified samples at different localisations are needed that are not included in a standard protocol of the OECD test guidelines. Taking the available evidence (consistency of the findings across several studies), differences in effective doses and uncertainties (standard methods may not represent the best practice to characterise the effects on bone histology and lack of a systematic microscopy of representative bone samples) the DS favours STOT RE 2.
RAC's response
RAC agrees with STOT RE 2 (teeth, bone). Please see the justification in the Opinion.

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2021	Belgium	Chemours Netherlands BV, for Fluorotelomers REACH consortium	Company-Importer	4
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment 6-2 FTOH CLH response 08-Apr-21.pdf				
Dossier Submitter's Response				
See above comment no. 2.				
RAC's response				
Noted. However, the attachment is not relevant to STOT RE hazard class.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2021	Belgium		MemberState	5
Comment received				
BE CA supports the proposed environmental classification for 6:2 FTOH as well as the approach taken for deciding on classifying for long-term hazard (based on NOECs and surrogate approach for the trophic level where no adequate NOEC is available): - No classification warranted for Aquatic Acute toxicity - Aquatic Chronic 2, H411 Several aquatic toxicity studies were considered not reliable (4) because there were too little details provided on the studies in the registration dossier. However all studies were conducted according to an OECD TG, with no deviations (following the registrant(s)), some of them GLP compliant, with performance of analytical monitoring, validity criteria were met according to the registrant(s), … Although not changing the proposed environmental classification, we were wondering if full study reports were requested from the registrant(s) and assessed by the DS because this might have led to the attribution of a higher reliability score for some studies. Now the NOEC for invertebrates is considered the lowest adequate chronic toxicity value and not the NOEC for algae (Desmodesmus subspicatus).				
Dossier Submitter's Response				
Thank you for your support on the classification proposal. We requested some tests from the registrant, which could not be provided, as there were not available for the registrant. Despite of this, the data rated with reliability 4 in the dossier would not change the classification as there were in the same range as the data used for classification. In addition, chronic toxicity data obtained for aquatic invertebrates and algae are not a factor of 2 different from each other.				
RAC's response				
RAC took note of the comment and the response.				

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2021	Sweden		MemberState	6
Comment received				
p 15-23: Aquatic Environmental hazards The Swedish CA agrees with the proposal that no acute aquatic environmental hazard classification is trigged for this substance. Acute aquatic toxicity data for all three trophic levels are available and indicate LC50/EC50/ErC50 >1 mg/L. Additionally, the Swedish CA agrees with the proposed long-term aquatic environmental hazard classification; Aquatic chronic 2, H411. The substance is not rapidly degradable, and the available chronic toxicity data indicate that NOEC is above 1 mg/L for both invertebrates and algae. However, no chronic toxicity data is available for fish. Therefore, the surrogate approach described in Table 4.1.0 (b) (iii) of the CLP Regulation should be used to decide if a long-term hazard classification may be warranted. Based on fish LC50 of 4.84 mg/L and the fact that the substance is not rapidly degradable a long-term				

aquatic environmental hazard classification of Aquatic chronic 2, H411, is warranted.
Dossier Submitter's Response
Thank you for your support on the classification proposal.
RAC's response
RAC takes note of the comment and the response.

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2021	United Kingdom	Health and Safety Executive	National Authority	7

Comment received

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol (CAS: 647-42-7)
It would be useful if the DS could present the available ecotoxicity data for the transformation products to support the conclusion that the substance is not rapidly degradable according to CLP criteria.

This ecotoxicity information could also affect the classification of the parent substance if it indicates that the degradants are more hazardous than the parent substance.

We note that a Fish Sexual Development Test n (FSDT) following OECD TG 234 using 6:2 FTOH was requested for the Substance Evaluations of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate (6:2 FTA, CAS 17527-29-6) and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate (6:2 FTMA, CAS 2144-53-8). The FSDT was due to be submitted by August 2020 and could potentially impact the classification of this substance CAS: 647-42-7. Please can the DS consider if this data is available and if it impacts the hazard classification?

Dossier Submitter's Response

Thank you for your comment.
The DS is aware of the OECD TG 234 study requested for the substance evaluation. At the time point of CLH dossier preparation, the results were not available. RAC may decide over the harmonised classification having regard to the results of the OECD TG 234 study.

Transformation product	Ecotoxicity data
perfluorobutanoic acid (CAS-No: 375-22-4)	Not registered under REACH. 48h-LC_{50} (daphnia) > 100 mg/L, no data available for fish and algae (Hoke et al. 2012) Not rapidly degradable
perfluoropentanoic acid (CAS-No: 2706-90-3)	Not registered under REACH 96h-LC_{50} (fish) = 32 mg/L, 48h-LC_{50} (daphnia) > 112 mg/L, 72h-E_rC_{50} = 99.2 mg/L (Hoke et al. 2012) Not rapidly degradable
perfluorohexanoic acid (CAS-No: 307-24-4)	Not registered under REACH (data from ammonium salt of perfluorohexanoic acid, CAS-No: 21615-47-4) Based on currently available data, criteria for classification as hazardous to the aquatic environment are not fulfilled (EC/LC_{50} and NOEC for all trophic levels > 1mg/L) (data summarized in restriction dossier for PFHxA, its salt and related substances)

5:3 polyfluorinated acid (CAS-No: 914637-49-3)	Not registered under REACH 48h-LC_{50} (daphnia) > 103 mg/L, 72h-E_rC_{50} = 53.3 mg/L, no data available for fish (Hoke et al. 2012)
4:3 polyfluorinated acid (CAS-No: 80705-13-1)	Not registered under REACH No data available
5:2 secondary alcohol (CAS-No: 914637-05-1)	Not registered under REACH No data available

Hoke R.A., Bouchelle L.D., Ferrell B.D., and Buck R.C. (2012): Comparative acute freshwater hazard assessment and preliminary PNEC development for eight fluorinated acids. Chemosphere 87 (7), 725-733. DOI: 10.1016/j.chemosphere.2011.12.066

RAC's response

RAC takes note of the comment and the response as well as the additional information provided.

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2021	France		MemberState	8

Comment received

FR supports the proposal to classify the substance tridecafluorooctan (n° CAS: 647-42-7) Aquatic Chronic 2, H411.
Page 16-17 - Degradation:
Adding QSAR information such as BIOWIN model to predict non-biodegradability as a part of expert judgement and weight of evidence can be of interest. The guidance on the application of the CLP criteria 2017 (p.571) states that the decision for not rapidly degradable may be supported by fulfilment of the following criteria: "the substance is predicted to be slowly biodegradable by scientifically valid QSARs,…".
Page 18 – Bioaccumulation:
We are of the opinion that the testing concentrations might be lower than the recommendation in the OECD 305 guideline (The concentration(s) of the test substance should be selected to be below its chronic effect level or 1% of its acute asymptotic LC50, within an environmentally relevant range and at least an order of magnitude above its limit of quantification in water by the analytical method used, p.12). It is also unclear if the standard BCF calculation had been adapted for exponential growth of the fish and normalized on a 5% lipid content. Could you please give a short explanation on these topics if possible?
Can you give an argumentation for not using QSAR BCFBAF results? Arnot & Gobas model suggest a BCF of 1500, although we understand that this model might not be appropriate for perfluorinated substances.

Dossier Submitter's Response

Thank you for your support on the classification proposal.
We have not used QSAR estimations as the models are only limited appropriate for per- and polyfluorinated substances.

Study Kurume Laboratory, 2002: lipid normalised BCF ≤ 80 (exposure level 1 µg/L) and = 102 (exposure level 10 µg/L); no information on growth in the study summary of the registration dossier
Study Kurume Laboratory, 2007: no information on lipid content and growth in the study summary of the registration dossier

RAC's response
RAC takes note of the comment and the response.

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2021	Belgium	Chemours Netherlands BV, for Fluorotelomers REACH consortium	Company-Importer	9
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment 6-2 FTOH CLH response 08-Apr-21.pdf				
Dossier Submitter's Response				
Please see response to comment 1.				
RAC's response				
Thank you for the OECD TG 234 study. RAC takes note of the additional information provided.				

PUBLIC ATTACHMENTS
1. 6-2 FTOH CLH response 08-Apr-21.pdf [Please refer to comment No. 1, 4, 9]