Committee for Risk Assessment

RAC

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

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26 November 2021

CLH-O-0000007052-84-01/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 Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **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**

The proposal was submitted by **Germany** and received by RAC on **18 January 2021.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany 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 **8 February 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **9 April 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Ifthekhar Ali Mohammed**

Co-Rapporteur, appointed by RAC: **Raili Moldov**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **26 November 2021** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

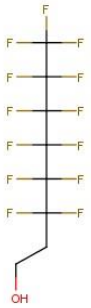
	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal[#]	TBD	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol	211-477-1	647-42-7	STOT RE 2 Aquatic Chronic 2	H373 (skeletal system) H411	GHS08 GHS09 Wng	H373 (skeletal system) H411			
RAC opinion	TBD	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol	211-477-1	647-42-7	STOT RE 2 Aquatic Chronic 1	H373 (teeth, bones) H410	GHS08 GHS09 Wng	H373 (teeth, bones) H410		M=1	
Resulting Annex VI entry if agreed by COM	TBD	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol	211-477-1	647-42-7	STOT RE 2 Aquatic Chronic 1	H373 (teeth, bones) H410	GHS08 GHS09 Wng	H373 (teeth, bones) H410		M=1	

[#]the DS agreed during the consultation to add "liver" as target organ: STOT RE 2; H373 (skeletal system, liver)

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol, hereinafter referred to with its abbreviation, **6:2 FTOH**, is registered under REACH for intermediate use only.



Structural formula of 6:2 FTOH

6:2 FTOH is a liquid (at 20 °C and 101.3 kPa) with a boiling point of 88 – 95 °C (at 28 – 30 mmHg), water solubility of 18.8 mg/L (at 22.5 °C) and Log K_{OW} of 4.54 (data from the REACH registration dossier).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) presented two 28-day studies in rats (an oral and an inhalation study), one oral 90-day study in rats, two oral one-generation studies (one each in rats and in mice), one oral combined repeated-dose and reproductive toxicity screening study in rats, and one oral prenatal developmental toxicity study in rats for the evaluation of STOT RE for 6:2 FTOH.

The DS proposed to classify 6:2 FTOH for STOT RE 2 based on effects observed in the 28-day study in rats (mottled teeth and delamination of the lower incisor tip surface at 25 mg/kg bw/d supporting STOT RE 1 [equivalent guidance value ≤ 30 mg/kg bw/d]) and in the one-generation study in mice (degeneration and atrophy of ameloblastic epithelium at 100 mg/kg bw/d, supporting STOT RE 2 [equivalent guidance value ≤ 134 mg/kg bw/d based on 67 days of exposure to females in the study]).

The DS proposed to specify skeletal system as the target organ with the following justification: "*The studies available did not present information on the undecalcified bone matrix due to fact that such investigations need special staining procedures and were not conducted in any of the studies available. The evidence on chronic fluorosis-related mottled/broken teeth should be taken as a surrogate for systemic fluorosis assuming that bone fluorosis (that could not be detected without appropriate methodology) was also present.*"

Comments received during consultation

Two MSCAs and a company submitted comments during the consultation. The comment by the company was not relevant to STOT RE. One MSCA requested further explanation for the choice

of category 2 as, in their view, the effects in the 28-day study point to category 1 and the discordance in results between 28 and 90-day studies should be discussed. The DS responded that, as opposed to only one 28-day study pointing to category 1, there are also three studies with longer duration that either support category 2 or no classification. The DS also noted that the effects on teeth were identified as gross pathological findings and in only some studies the teeth were microscopically examined on decalcified H&E stained paraffin sections. The DS further added that, 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 would be needed and these are not included in the standard protocols of the OECD test guidelines.

The other MSCA supported the proposed STOT RE 2 classification. However, they considered that specifying teeth as the target organ could be appropriate. The MSCA reasoned that effects on bone may have occurred in the animals, but any such effect had not been substantiated in the studies (due to lack of evaluation of bone in the studies, except in the mice study). The MSCA further claimed that 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 was a borderline case. The MSCA also commented that, based on the liver effects observed in most of the studies, a classification as STOT RE 2 should also be considered for liver toxicity. The DS agreed to adding liver as the second target organ. The DS also agreed that specifying teeth instead of skeletal system as the primary target organ is an option. In the DS's view fluorosis should be considered as a systemic adverse effect affecting the whole skeletal system (bones and teeth) and mottled teeth are considered as an indicator for the systemic disorder of bone metabolism. Therefore, they preferred specifying skeletal system as the primary target organ.

Assessment and comparison with the classification criteria

In the CLH report, the DS identified skeletal system as the target organ for STOT RE and in the RCOM agreed to liver also being a target organ.

In the 28-day oral study (Hita Laboratory, 2007; unpublished), equivalent to OECD TG 407 and in compliance with GLP, 6:2 FTOH was administered by gavage to 5 rats/sex/dose at 5, 25 and 125 mg/kg bw/d. There were also two (vehicle and high dose) 14-day recovery groups with 5 animals/sex.

There were no mortalities in the study. Body weight and food consumption data were not presented in the CLH report. Clinical observations included decreased locomotor activity, decreased respiration rate and (on day 7 only) incomplete eye opening in the males in the 125 mg/kg bw/d group during the dosing period.

5 mg/kg bw/d group: No effects.

25 mg/kg bw/d group: Discoloration of the incisors (2 M, 3 F), mottled teeth (1 M, 0 F), increase in relative liver weight (F only) and enlargement of liver (F only) were observed.

125 mg/kg bw/d group: Discoloration of the incisors (5 M, 5 F), mottled teeth (3 M, 1 F) and decreased iron pigments of the ameloblasts at maturation stage in the incisors (1 M, 2 F) were observed. These effects persisted in the recovery group. In addition, delamination of the lower incisors tip surface (4 M, 5 F), an irregular alignment of the ameloblasts at maturation stage in the incisors (3 F) and cell infiltration of the gingiva were newly observed in the recovery group.

Liver effects at 125 mg/kg bw/d group included: significant increase in relative weight (M), increased absolute and relative weights (F; the increased relative weight remained statistically significant in the recovery group), increased ALT and ALP activities (M, F),

increased total cholesterol (F only), enlargement of liver (M, F), periportal/diffuse liver cell hypertrophy (5 M, 5 F) were observed at the end of dosing period but disappeared/improved in the recovery group.

Support for STOT RE classification: The equivalent guidance values for 28-day oral study are ≤ 30 mg/kg bw/d for Cat. 1 and ≤ 300 mg/kg bw/d for Cat. 2. RAC considers the dental effects starting at 25 mg/kg bw/d support Cat. 1. The severity of these effects considerably increased in the next dose level and the result was also supported by histopathological findings. RAC considers the liver toxicity as adaptive responses that were reversed at the end of recovery period and thus support no classification.

In the 28-day inhalation study (Dupont, 2011; unpublished), according to OECD TG 412 and in compliance with GLP, 6:2 FTOH was administered via whole-body exposure to 10 rats/sex/dose at 1, 10 and 100 ppm for 6 h/d (5 days/week). There were two (control and high dose) 1-month recovery groups with 10 animals/sex/dose.

There were no treatment-related mortalities or effects on body weights and food consumption. Clinical observations were limited to decreased locomotor activity in males during the 4th week of exposure period in the high dose group (100 ppm corresponding to 1.49 mg/L) that was reversed during recovery period.

In the high dose group, there was increased lamination of dentin of the incisors and incomplete decalcification of enamel of the incisors, and the bone trabeculae in tibia and femur that remained during the recovery period.

Liver effects observed in the high dose group were increased absolute and relative liver weight, increased mean serum bilirubin and only in females, increased ALT. All these effects were reversed during the recovery period.

Support for STOT RE classification: The equivalent guidance value for 28-day inhalation study is > 0.6 and ≤ 3 mg/L/6h/d for Cat. 2. Although the details on the effects are limited in this study, RAC considers the dental and bone effects at 1.49 mg/L supports Cat. 2. Since the liver effects in this study were reversible and with no correlated histopathological findings, RAC considers these to support no classification.

In the 90-day oral study (Charles River Laboratories, 2012; unpublished and Serex *et al.*, 2014), according to OECD TG 408 and in compliance with GLP, 6:2 FTOH was administered by gavage to 10 rats/sex/dose at 5, 25, 125 and 250 mg/kg bw/d. There were also recovery groups of 1-month (control and high dose; 10 animals/sex/dose) and 3-months (all dose levels; 5 animals/sex/dose). Fluoride concentrations were determined in plasma and urine.

Treatment-related mortality mostly attributed to kidney degeneration and necrosis was observed in the 125 mg/kg bw/d (1/25 F at day 62) and 250 mg/kg bw/d groups (6/25 M and 13/25 F from day 22 to 84). Clinical observations were also limited to 125 mg/kg bw/d and 250 mg/kg bw/d groups. The mean body weight changes were about 9% (M) and 3% (F) of the control values and were not dose dependent.

Whitened teeth and increased incidence in missing/broken/misaligned incisors were observed in the 125 and 250 mg/kg bw/d groups. Effects on ameloblastic epithelium of the teeth were observed in the 250 mg/kg bw/d group (M only, but there was only 1 F left in this group) which were also seen after 1-month recovery period but resolved by 3-months.

There were dose-related statistically significant increases in absolute and relative liver weights at ≥ 25 mg/kg bw/d groups in males or females. Histopathology of liver revealed minimal severity effects in males at ≥ 125 mg/kg bw/d groups and in females at ≥ 25 mg/kg bw/d groups. These effects included single-cell necrosis, vacuolization, oval/biliary hyperplasia, hepatocellular hypertrophy and periportal inflammation. No quantitative details on the effects were reported in

the Serex *et al.* (2014) publication. In males, none of the effects were noted at the 1-month recovery sacrifice. In females, most of these effects were not present at the 1-month recovery sacrifice, and by 3 months only a few females in the 125 and 250 mg/kg bw/d groups had biliary hyperplasia.

***Table**: Absolute and relative liver weights in the 90-day oral study (adapted from Serex et al., 2014)*

Dose in mg/kg bw/d (no. of animals)		Control (10/sex)	5 (10/sex)	25 (10/sex)	125 (10M, 9F)	250 (8M, 1F)
Males	Weight (g)	15.94 ± 1.90	16.09 ± 1.90	16.62 ± 2.02	19.09 ± 1.89*,b	22.84 ± 2.39*,a,b
	Ratio (%)	2.95 ± 0.26	3.04 ± 0.15	3.26 ± 0.16*,b	3.94 ± 0.17*,b	4.61 ± 2.39*,c
Females	Weight (g)	8.44 ± 0.70	8.67 ± 0.92	9.47 ± 0.90*	12.50 ± 1.06*	14.62c
	Ratio (%)	3.20 ± 0.23	3.13 ± 0.19	3.43 ± 0.31	4.45 ± 0.30*,a,b	5.58*,c

a: Parameter no longer statistically significantly different from control rats 1 month after cessation of dosing.
b: Parameter no longer statistically significantly different from control rats 3 months after cessation of dosing.
c: Parameter statistically significantly higher than control at 1 but not 3 months after cessation of dosing.
* statistically significant

There was a dose-related statistically significant increase in urine fluoride at ≥ 25 mg/kg bw/d groups in males or females. There was a dose-related significant increase in plasma fluoride in males (≥ 25 mg/kg bw/d groups) and females (≥ 125 mg/kg bw/d groups). Plasma fluoride was partially reversible after approximately 1 month of recovery and completely reversible after 3 months of recovery.

***Table**: Plasma and urine fluoride levels in the 90-day oral study (adapted from Serex et al., 2014)*

Dose in mg/kg bw/d (no. of animals)		Control (10/sex)	5 (10/sex)	25 (10/sex)	125 (10M, 9F)	250 (8M, 1F)
Plasma fluoride (µg/mL)	Males	0.1 ± 0	0.1 ± 0	0.2 ± 0*	0.7 ± 0.2*	0.9 ± 0.2*a
	Females	0.1 ± 0	0.1 ± 0	0.1 ± 0	0.6 ± 0.2*	1.1a,b
Urine fluoride (µg)	Males	11.3 ± 3.1	106 ± 39	482 ± 146*	1890 ± 407*	3602 ± 670*
	Females	6.0 ± 1.9	39 ± 13	18 ± 64*	1206 ± 288*	2921

a: 0.2 µg/mL plasma fluoride after 1 month recovery; b: 0.1 mg/µL or not detected after 3 month recovery;
* statistically significant

Support for STOT RE classification: The guidance value for 90-day oral study is > 10 and ≤ 100 mg/kg bw/d for Cat. 2. Although there were no dental effects in this study at 25 mg/kg bw/d, the effects (missing/broken/misaligned incisors) at the next dose level of 125 mg/kg bw/d were very severe. Also, the plasma and urinary fluoride levels were dose-dependently increased with reaching statistical significance already at 25 mg/kg bw/d. Therefore, RAC considers the dental effects in this study to support Cat. 2. In females, the increased liver weight was correlated with histopathological findings at ≥ 25 mg/kg bw/d. However, due to lack of quantitative details on the liver effects, RAC considers the liver effects in this study not sufficient for classification.

In the one-generation oral study in rats (Charles River Laboratories, 2008; unpublished and O'Connor *et al.*, 2014), according to OECD TG 415 and in compliance with GLP, 6:2 FTOH was administered via gavage to 20 animals/sex/dose at 5, 25, 125 and 250 mg/kg bw/d. The males were exposed for about 84 days and females for about 126 days in total.

Treatment-related mortalities were observed in the 125 mg/kg bw/d group (3 M) and in the 250 mg/kg bw/d group (3 M, and 13 F; of which 4 during premating, 5 during gestation and 4 during lactation period). In the 250 mg/kg bw/d group, the mean body weight gain during premating period was -14% (M) and -10% (F) compared to controls.

The following dental effects with statistically significant increase in incidences were observed in parental males and females at 125 and 250 mg/kg bw/d groups: whitened teeth, missing teeth, misaligned or broken teeth and overgrown incisors. These effects were mostly observed during late premating period for males and during gestation and lactation periods for females. No further details for e.g., on the number of animals affected in each group were presented in the CLH report. No macroscopic dental effects were observed in the pups (on PND 22).

Parameters relevant to liver toxicity were not examined in the study.

Support for STOT RE classification: The equivalent guidance value for 84 days oral exposure (to males) is ≤ 107 mg/kg bw/d for Cat. 2. At 125 mg/kg bw/d there were severe dental effects (missing/misaligned/broken teeth) in males. While noting that the guidance values are not meant to be strict demarcation values, RAC considers the severity of dental effects observed in this study to support Cat. 2.

In the one-generation oral study in mice (DuPont, 2013; unpublished and Mukerji *et al.*, 2015), according to OECD TG 415 and in compliance with GLP, 6:2 FTOH was administered via gavage to 15 animals/sex/dose at 1, 5, 25 and 100 mg/kg bw/d. The males were exposed for about 84 days and females for about 67 days in total.

Treatment-related mortalities (1 M, 2 F) were observed in the 100 mg/kg bw/d group during premating or gestation periods. In the 100 mg/kg bw/d group, the final mean body weight was -5% in males and there was no effect on females during the premating period compared to controls.

In the 100 mg/kg bw/d group the following effects on the incisors were observed: degeneration and atrophy of ameloblasts characterized by segmental disorganization and attenuation of ameloblastic epithelium of the incisors; lamination of dentin characterized by the presence of concentric basophilic rings within the dentin of these teeth; incomplete decalcification of enamel and dentin characterized by an increase in the observed presence of basophilic, mineralized debris in the enamel space of the incisor between the dentin and the gingiva. Furthermore, consistent with fluoride exposure, an incomplete decalcification of nasal bones in some animals was observed in the 100 mg/kg bw/d group. The numbers of animals showing effects on the incisors and nasal bones were not presented in the CLH report.

In the 100 mg/kg bw/d group, the absolute liver weights were increased by 6% (M) and 13% (F) and the relative liver weights (statistically significant) were increased by 13% (M) and 24% (F) compared to controls. The changes in liver weights were correlated with histopathological findings (see table below) including the adverse single cell necrosis in 12 of 15 animals of both sexes.

***Table**: Histopathological findings of liver in the one-generation oral study in mice (Table 6 from Mukerji et al., 2015)*

Dose (mg/kg/day): no. examined	Male					Female				
	0(15)	1(15)	5(15)	25(15)	100(15)	0(15)	1(15)	5(15)	25(15)	100(15)
Hypertrophy, hepatocellular	0	0	9	10	15	0	0	13	12	13
Mitotic figures, increased	0	0	0	0	5	0	1	0	1	10
Oval cell hyperplasia	0	0	0	0	15	0	0	0	2	12
Cystic degeneration	0	0	0	0	0	0	0	1	1	7
Single cell necrosis	0	0	0	0	12	2	1	1	1	12
Infiltrate, mononuclear (oval cell associated)	0	0	0	0	15	0	0	0	0	10
Pigment, increased	0	0	0	0	15	0	0	0	0	0

Support for STOT RE classification: The equivalent guidance value for 67 days oral exposure (to females) is ≤ 134 mg/kg bw/d for Cat. 2. RAC considers the dental effects, and bone effects (incomplete decalcification of nasal bones) observed in this study at 100 mg/kg bw/d to support Cat. 2. Although histopathological findings were observed in the liver, no information on severity of these effects is available. Thus, RAC proposes no classification for liver effects.

In the oral combined repeated-dose and reproductive toxicity screening study (WIL Research Laboratories, 2005; unpublished), according to OECD TG 422 and in compliance with GLP, 6:2 FTOH was administered via gavage to 10 rats/sex/dose at 25, 75 and 225 mg/kg bw/d. Additional 5 rats/sex/dose were allocated to recovery groups (control and high dose). The males in the study were exposed to at least 32 days and the females to at least 39 days.

Treatment-related mortalities (1/15 M and 11/15 F) were observed in the 225 mg/kg bw/d group. Higher liver weight and hepatic centrilobular hypertrophy in males was observed in the 225 mg/kg bw/d group. No further data on the liver effects was reported in the CLH report.

Teeth were not examined in the study.

Support for STOT RE classification: The equivalent guidance value for oral exposure of around 30 days is > 30 and ≤ 300 mg/kg bw/d , and for 39 days is > 23 and ≤ 231 mg/kg bw/d for Cat. 2. RAC considers the liver effects reported in this study as not severe enough for classification.

In the oral prenatal developmental toxicity (DuPont, 2008; unpublished and O'Connor *et al.*, 2014), according to OECD TG 414 and in compliance with GLP, 6:2 FTOH was administered via gavage from GD 6 – 20 at 5, 25, 125 and 250 mg/kg bw/d. No treatment-related mortalities were observed. Teeth, bone, and liver parameters were not examined.

Overall, significant effects on teeth were consistently observed in the studies at levels supporting STOT RE 2 (except one 28-day oral study supporting STOT RE 1 but the severe dental effects were only observed at levels supporting STOT RE 2 in this study and in the other studies). The effects on bone (incomplete decalcification in nasal bone, tibia and femur suggesting significant morphological changes) in the only two studies that examined it also supports STOT RE 2. In line with the DS's view, RAC considers the evidence on chronic fluorosis-related mottled/broken teeth can be taken as an indicator of skeletal fluorosis characterised by metabolic bone disorder. 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 'bones' as target organs. Liver toxicity manifested as, in particular the adverse single cell necrosis, was also observed in two sub-chronic exposure studies at levels supporting STOT RE 2. However, in the absence of quantitative details on these effects, RAC proposes no classification for liver effects.

RAC notes that also mortalities were observed at dose levels below (Mukerji *et al.*, 2015) or close to (Serex *et al.,* 2014, O'Connor *et al.*, 2014 and WIL, 2015) the guidance value for Cat. 2.

In conclusion, RAC proposes STOT RE 2; H373 (teeth, bones) for 6:2 FTOH.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

There is no current entry in Annex VI of the CLP Regulation for the substance 6:2 FTOH.

The DS proposal was to classify the substance as Aquatic Chronic 2, H411, the substance being not rapidly degradable, based on the surrogate approach and the lowest EC_{50} obtained with *Pimephales promelas* (4.84 mg/L, mean measured (mm)) due to no chronic aquatic toxicity data available for the most acutely sensitive species (fish).

The physico-chemical characteristics show that 6:2 FTOH has moderate water solubility (18.8 mg/L at 22.5 °C) and vapour pressure of 18 Pa at 25 °C, indicating moderate to high volatility.

Degradation

There are several aquatic degradation / transformation products of 6:2 FTOH. In an aerobic river sediment system 5:3 acid (F(CF2)5CH2CH2COOH, 22.4 mol%), perfluoropentanoic acid (PFPeA, 10.4 mol%), perfluorohexanoic acid (PFHxA, 8.4 mol%), perfluorobutanoic acid (PFBA, 1.5 mol%), 6:2 fluorotelomer saturated acid (6:2 FTCA, <1 mol%), 6:2 fluorotelomer unsaturated acid (6:2 FTUCA, <1 mol%), 4:3 acid (F(CF2)4CH2CH2COOH, 2.7 mol%), 5:2 ketone [F(CF2)5C(O)CH3, 1.5 mol%), and 5:2 sFTOH (F(CF2)5CH(OH)CH3, 20.2 mol%) were detected after 100 days (Anonymous, 2013). In a mixed aerobic bacterial culture developed from activated sludge, 6:2 FTOH degraded at day 28 into 6:2 FTUCA (25%) and 5:2 sFTOH (17%) as the two dominant metabolites with 6:2 FTCA (5.7%), 5-3 acid (5.5%), PFHxA (5.1%), and PFBA and PFPeA each less than 0.5% yield. (Anonymous, 2013)

A summary of the relevant information on rapid degradability is provided in Table 11 of the CLH report.

Abiotic degradation

No data is provided on the hydrolysis of the substance.

Biodegradation

Rapid biodegradation

No reliable/ valid studies are presented on ready biodegradability for 6:2 FTOH. Available data of questionable reliability according to OECD TG 301D indicated low degradation (5% after 28 days, Anonymous, 2010; Anonymous, 2000).

The recovery of 6:2 FTOH and quantifiable transformation products of 71-88 mol% of initially applied 6:2 FTOH in an aerobic river sediment system. The primary DT_{50} in sediment system was estimated to be 1.8 days. After the initial rapid decrease, the 6:2 FTOH concentration was relatively constant after day 28 (Anonymous, 2013).

The concentration of 6:2 FTOH decreased to 1.6-2.8% after 7 days (primary biodegradation) in a study with mixed aerobic bacterial culture developed from activated sludge (Anonymous, 2010). However, due to the adaption of the inoculum the study is not considered valid for classification purposes.

The DS concluded that since there is no clear evidence of rapid degradation (only primary degradation) and a lack of available data on the fate and hazardous properties of the degradation products, 6:2 FTOH does not fulfil the criteria to be considered as rapidly degradable in the aquatic environment, according to the CLP criteria.

Bioaccumulation

A summary of the available information on bioaccumulation is provided in Table 12 of the CLH report.

A Log K_{OW} of 4.54 has been determined according to OECD TG 107 (Anonymous, 2008).

Two OECD TG 305 fish bioconcentration test results have been provided showing whole body wet weight based BCF values of ≤ 36 (exposure level 1 µg/L) and 46 (exposure level 10 µg/L) at steady state and 24 - 99 (exposure level 1 µg/L) and 8.4 - 58 (exposure level 10 µg/L) with *Cyprinus carpio* after 28 days of exposure respectively (Anonymous, 2002; Anonymous, 2007).

The DS concludes that 6:2 FTOH is considered to have low potential for bioaccumulation in the aquatic environment due to the higher preference given in the CLP Regulation to experimental data (BCF values below the threshold value of 500) over Log K_{OW} (meeting the CLP trigger value of Log K_{OW} ≥ 4).

Aquatic toxicity

Aquatic acute toxicity

A summary of the relevant information on aquatic acute toxicity is presented in Table 13 of the CLH report.

Aquatic acute toxicity studies are presented for all three trophic levels: fish, invertebrates, algae and other aquatic plants.

One valid OECD TG 203 acute fish toxicity study is available with *Pimephales promelas* in a static test design presenting an LC_{50} of 4.84 mg/L (mm) after 96 h of exposure (Anonymous 1, 2007).

For invertebrates, one reliable acute study has been given. The *Daphnia magna* OECD TG 202 immobilisation test provided an EC_{50} of 7.84 mg/L (mm) after 48 h exposure (Anonymous, 2007).

One reliable OECD TG 201 study is available with *Pseudokirchneriella subcapitata* showing a 72 h E_rC_{50} value of 14.8 mg/L (mm) (Anonymous, 2007).

The studies provided with a questionable reliability due to lack of detailed information on the test design were all in similar range for all trophic levels. According to the provided valid studies, fish are found to be the most sensitive species. The lowest EC_{50} is obtained with *Pimephales promelas* (4.84 mg/L (mm)) not meeting the CLP classification criteria for aquatic acute hazards so the **DS proposed not to classify 6:2 FTOH for acute hazards based on the L(E)C_{50} ≥ 1 mg/L in CLP Table 4.1.0 (a).**

Aquatic chronic toxicity

Valid data for aquatic chronic toxicity are only presented for two trophic levels: invertebrates and algae. No long-term fish test was available at the time of the CLH dossier submission.

The OECD TG 211 reproduction test (semi-static, 21 d) with *Daphnia magna* resulted in a NOEC of 2.16 mg/L (mm) based on adult survival, total live young per female, total immobile young per surviving female and length and weight of surviving females.

The OECD TG 201 study with *Pseudokirchneriella subcapitata* resulted in a NOE_rC of 2.22 mg/L (mm). The other two studies presented for algae and aquatic plants were not considered to meet the validity criteria and were in the same order of magnitude. (Anonymous, 2007)

Since no chronic aquatic toxicity data was available for fish but fish species are acutely the most sensitive endpoint, the DS considered based on a surrogate approach and for a not rapidly degradable substance that 6:2 FTOH **fulfils the criteria for classification as Aquatic Chronic Category 2, H411 based on the L(E)C_{50}> 1 and ≤ 10 mg/L in CLP Table 4.1.0 (b)(iii).**

Comments received during consultation

One company(importer) supported the classification proposal and submitted information on an ongoing OECD TG 234 study still being, at that time, conducted.

Three MSs supported the proposed classification and the classification approach based on the NOECs, the substance being not rapidly degradable and the use of the surrogate approach for the trophic level where no adequate NOEC is available (fish species).

The actual validity of the studies provided was questioned by one MS as no full study reports seemed to be available for assessment. The MS also reported a non-valid invertebrate study indicating a NOEC lower than the NOEC values from the valid invertebrate and algae studies but considered this to be of low relevance as the values would not change the classification proposal. The DS noted that detailed test results were requested from industry but were not provided. The proposed chronic classification would be the same as the proposed one, as all the study results provided are in the same range. The DS additionally noted that the results from the studies with a reliability of 3 and 4 were not used in the derivation of the classification proposal.

One MS suggested to use QSAR modelling to support biodegradation and bioconcentration data. The DS considered models of only limited relevance for per- and polyfluorinated substances. The same MS also noted the test concentrations might be lower than the recommended in OECD TG 305 and it was unclear if the standard BCF calculation had been adapted for growth of fish and normalised on a 5% of lipid content. The DS informed the MS on lipid normalised BCF values and noted that no information on growth was available, as well as on the lipid content from another study.

One MS requested additional information on the transformation products to support the conclusion on the substance being not rapidly degradable and noted that the substance's hazard profile could be also driven by potentially more hazardous transformation products. The MS also asked for the outcome of an additional, ongoing OECD TG 234 study to be taken into account. The DS provided the additional information on the transformation products supporting the presented outcome of the classification proposal and showing that the transformation products are also considered as not rapidly degradable and do not pose a greater hazard to aquatic environment based on the available data.

The DS did not have the full study report of the additional OECD TG 234 study available at the time of the submission and left the results to be interpreted by RAC.

Comments received during the ad hoc consultation

Industry eventually provided the report of the OECD TG 234 study with fish and an ad hoc consultation was held. For confidentiality reasons only an extended robust study summary from the REACH Registration dossier was placed under the consultation. The full study report was made available for RAC for evaluation.

Three MSs supported the use of OECD TG 234 study results indicating a classification of Aquatic Chronic 1, H410 and an M-factor of 1.

One MS noted the uncertainties in the validity criteria of this study that may not allow reaching the highest reliability score and that the lack of another chronic study on vertebrates (which may be the most sensitive species as seen in acute studies) may have led to a lower NOEC and, thus, a higher M-factor. However, the MS considered the reliability of the study being acceptable and sufficient for classification purposes.

One MS also noted the lack of details in the study summary provided and questioned meeting the OECD TG 234 validity criteria due to, for example, variation in the measured concentrations.

The same MS mentioned that the NOEC for hatching success based on geometric mean measured concentration (0.0231 mg/L) should be used for the classification, due to problems maintaining and achieving the nominal concentrations in the test system.

Two MSs noted the overall study lowest NOEC value of 0.0137 mg/L (mm). One of them suggested that the lowest chronic fish toxicity endpoint relevant for the purpose of hazard classification is the 122-d NOEC of 0.0231 mg/L (mm) for hatching success. It was also mentioned the EC_x values would be useful to determine the chronic classification outcome. The MS also suggested to take into account the review of the Evaluating MS for the parallel REACH Substance Evaluation process, once available.

One MS commented on the self-classification of the substance 6:2 FTMA which seems to be based on the lowest NOEC value of 0.0162 mg/L from the new OECD TG 234 study with 6:2 FTOH and was unsure of the calculation and the validity of this value.

Animporter took note of the OECD TG 234 study results and proposed to classify 6:2 FTOH as Aquatic Chronic 1, H410 with an M-factor of 1, based on a lowest NOEC value of 0.0137 mg/L.

Assessment and comparison with the classification criteria

Comparison with the criteria

The CLH report did not include information on the hydrolysis of 6:2 FTOH and behaviour in the water-sediment system, as well as ready biodegradation.

According to the available data presented by the DS on primary degradation of the substance, the lack of sufficient information on the hazardous properties of the aquatic degradation / transformation products and considering the criteria on rapid degradability defined in Section 4.1.2.9.3 of the CLP Regulation indicating that *primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment*, RAC agrees to consider 6:2 FTOH as **not rapidly degradable** for classification purpose.

RAC notes that no data have been provided as part of the CLH dossier showing toxicity of the degradation products and limited information has been provided as part of the consultation round. RAC also notes that a known longer-term degradation product is PFHxA with an available restriction proposal and RAC opinion (https://www.echa.europa.eu/documents/10162/8fa51c6a-70e4-1a20-5170-d34e58771a5a). RAC considered PFHxA as a very persistent substance in the environmental compartments. According to the degradation studies provided in the CLH dossier, in the mixed aerobic bacterial culture the metabolites' concentrations reached steady-state after 14–28 days and at day 28 concentration of PFHxA was 5.1% (Anonymous, 2010b). The study in aerobic river sediment system does not specify the time of the steady state of the transformation products but after 100 days 8.4 mol% PFHxA was detected (Anonymous, 2013).

Regarding bioaccumulation, RAC notes the available experimental BCF and Log K_{OW} data and considers the information sufficient to come to conclusion on the bioaccumulation potential of the substance in the aquatic compartment. According to the Section 4.1.2.8 of the CLP Regulation, experimentally determined BCF values provide a better measure and shall be used in preference to partition coefficients, if available. Therefore, RAC agrees with the DS and concludes that 6:2 FTOH has **no potential for bioaccumulation** based on the available information on the BCF in fish (in the range of 24 - 99 (1 µg/L) and 8.4 - 58 (10 µg/L)) that are well below the cut-off value of 500.

RAC agrees with the DS that the most sensitive fish species LC_{50} value was that for *Pimephales promelas* (equal to 4.84 mg/L). Based on this study, but also all the other acute data that can

be considered scientifically robust and reliable to be used for classification purposes, RAC concludes that **no classification for aquatic acute hazards** is warranted for 6:2 FTOH.

RAC took into account the results of the additional OECD TG 234 fish study provided with *Oryzias latipes* as the test species and considers the study results valid for classification purposes despite minor discrepancies from the validity criteria. The most sensitive parameter (VTG concentration in males) has not been chosen due to VTG being only a mechanistic parameter and a measure for determining endocrine effects not the adverse effects for fish e.g. growth, survival or hatching success etc. RAC refers to previous similar conclusions on Triadimenol (ISO); α-tert-butyl-β-(4-chlorophenoxy)-1H-1,2,4-triazole-1-ethanol (EC: 259-537-6, CAS: 55219-65-3).

RAC notes that the outcome of the proposed classification would not change even if a lower available NOEC value, for example one based on the male VTG concentration, would be used and notes that the details of the calculations based on the nominal and mean measured concentrations were not available as part of the full study report. Finally, RAC points out that preference was given to the use of EC_{10} values compared to NOECs when applying chronic classification procedure. However, no statistical analysis has been performed to determine the ECx.

Thus, the lowest chronic fish toxicity endpoint is the 122-d NOEC of 0.0231 mg/L (gm) for hatching success that leads to an Aquatic Chronic 1 classification with an M-factor of 1 for 6:2 FTOH.

Taking into account that the chronic fish study was not available for the DS at the time of the submission of the CLH report, RAC does not support the originally proposed classification of Aquatic Chronic 2, H411 based on the surrogate approach. As reliable chronic data are now available for all trophic levels, the classification is based on CLP Table 4.1.0 (b)(i). Therefore, RAC proposes to consider the lowest chronic endpoint as the 122-day NOEC for *Oryzias latipes* of 0.0231 mg/L (mm) based on hatching success, resulting in a classification of **Aquatic Chronic 1, H410** for 6:2 FTOH. According to Table 4.1.3 in CLP Regulation an **M-factor** of **1** for a **not rapidly degradable** substance is warranted between the range of 0.01 and 0.1 mg/L.

RAC notes that if additional data become available either on the biodegradation, bioaccumulation potential and the degradation products in the environment and acute or chronic toxicity of 6:2 FTOH and its metabolites, the classification could be reconsidered.

ANNEXES:

Annex 1 The 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 (excluding confidential information).