CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

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**

Index Number: **n.a.**

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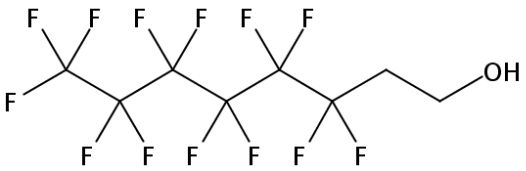
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol
Other names (usual name, trade name, abbreviation)	6:2 FTOH
EC number (if available and appropriate)	211-477-1
EC name (if available and appropriate)	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol
CAS number (if available)	647-42-7
Molecular formula	C8H5F13O
Structural formula	
SMILES notation (if available)	OCCC(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)F
Molecular weight or molecular weight range	364.1 g mol^{-1}

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
See table 1			

Table 3: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
-				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 4: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
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	-		
Resulting Annex VI entry if agreed by RAC and COM					STOT RE 2 Aquatic Chronic 2	H373 (skeletal system) H411	GHS08 GHS09 Wng	H373 (skeletal system) H411	-		

Table 5: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation		
Germ cell mutagenicity		
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure	Harmonised classification proposed	**Yes**
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Harmonised classification proposed	**Yes**
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no information available if this compound had been previously discussed by the TC C&L.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Requirement for harmonised classification by other legislation or process.

Further detail on need of action at Community level

The German CA investigated the possibility to identify 6:2-FTOH as substance of very high concern. A prerequisite to fulfil the criteria for toxicity is the harmonised classification and labelling as STOT RE 2.

Disagreement by DS with current self-classification

Notified classification and labelling are inconsistent and contradictory as seen below (as of 09.09.2020):
Acute Tox. 4 (H302) = 92 of 166
STOT RE 2 (H373) = 36 of 166
STOT SE 3 (H335) = 68 of 166
STOT RE 1 (H372) = 1 of 166
Skin Irrit. 2 (H315) = 68 of 166
Eye Irrit. 2 (H319) = 68 of 166
Aquatic Chronic 2 (H411) = 23 of 166
Not classified = 6 of 166

5 IDENTIFIED USES

According to the registration dossier the compound is used as intermediate.

6 DATA SOURCES

The following search terms were used:
3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctan-1-ol, 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanol, 1,1,2,2-Tetrahydroperfluoro-1-octanol, 1H,1H,2H,2H-Perfluorooctanol, 1H,1H,2H,2H-Perfluorooctan-1-ol, 1-Octanol, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-, 6:2 fluorotelomer alcohol, 6:2 FTOH, 6-2-fluorotelomer alcohol.

The following data sources were used: Pubmed, Web of Science, Scopus, Embase, SpringerLink, Wiley online Library, Taylor & Francis.

7 PHYSICOCHEMICAL PROPERTIES

Table 6: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101,3 kPa	liquid	REACH registration dossier	Visual observation
Melting/freezing point	-33.09 °C at atmospheric pressure	REACH registration dossier	According to OECD Guideline 102 Differential scanning calorimetry
Boiling point	88-95 °C at 28-30 mmHg	Day, Richard I.; GB 994607 1965 CAPLUS, cited from Scifinder	
Relative density	1.6782 g/cm^2 at 25 °C	Day, Richard I.; GB 994607 1965 CAPLUS, cited from Scifinder	
Vapour pressure	18 Pa at 25 °C (Gas-phase NMR) 44 Pa at 25 °C (Scott Method) 108 Pa at 35 °C (Gas Saturation Method)	REACH registration dossier	
Water solubility	18.8 mg/L at 22.5 °C	REACH registration dossier	Equivalent or Similar to OECD Guideline 105 flask method
Partition coefficient n-octanol/water	Log Pow: 4.54	REACH registration dossier	Equivalent or Similar to OECD Guideline 107 shake-flask method to: flask method

8 EVALUATION OF PHYSICAL HAZARDS

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.2 Skin corrosion/irritation
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.3 Serious eye damage/eye irritation
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.4 Respiratory sensitisation
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.5 Skin sensitisation
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.6 Germ cell mutagenicity
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.7 Carcinogenicity
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.8 Reproductive toxicity
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.9 Specific target organ toxicity-single exposure
This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

10.10 Specific target organ toxicity-repeated exposure

Table 7: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
"28-day Repeated Dose Toxicity Study in Mammalian Species" according to Notification No 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No 2 of the Manufacturing Industries Bureau, METI & No 031121002 of the Environmental Health Departement, MOE. Equivalent to OECD TG 407 Reliability 2 Rats, Crl:CD(SD) at 5 weeks of age, males and females, Five animals/sex/dose No data on fluoride concentrations in plasma, urine, dentin or bone matrix. No histopathology data on the trabecular bone (only decalcified bone medullary cavity examined).	Oral study, 5, 25 and 125 mg/kg body w/day and a vehicle control group. The substance was dissolved in olive oil (vehicle) and applied daily by gavage. 28 days of treatment. Additional animals were used for two recovery groups (vehicle and 125 mg/kg body w/day). The recovery period was 14 days. In compliance with GLP. The purity of 6:2 FTOH was 99.8 %.	Decreased locomotor activity, decreased respiration rate and (on day 7 only) incomplete eye opening in the males in the 125 mg/kg group was observed during the dosing period. Discoloration of the incisors was observed in two of five male animals in the 25 mg/kg bw/d group and in ten of ten male animals in the 125 mg/kg bw/d group. Mottled teeth were noted in one of five male animals in the 25 mg/kg bw/d group and eight of ten male animals in the 125 mg/kg bw/d group. In the recovery period discoloration of the incisors and mottled teeth were observed in five of five males in the 125 mg/kg bw/d recovery group. A delamination of the low incisor tip surface was observed in four of five males in the 125 mg/kg bw/d recovery group. At the termination of the dosing period, relative liver weight was significantly increased in the 125 mg/kg bw/d group (males). At the termination of the recovery period, relative testis weights were significantly increased in the 125 mg/kg bw/d group. Decreased iron pigments of the ameloblasts at maturation stage was observed in the incisor of one male rat of the 125 mg/kg bw/d group at the termination of dosage and in one male rat of the 125 mg/kg bw/d recovery group. All five male rats of the 125 mg/kg bw/d group showed periportal hypertrophy of the hepatocytes in the liver. Discoloration of the incisors was observed in three of five female animals in the 25 mg/kg bw/d group and in ten of ten female animals in the 125 mg/kg bw/d group. Mottled teeth were observed in six of ten animals in the 125 mg/kg bw/d group. In the recovery period discoloration of the incisors and mottled teeth and delamination of the low incisor tip surface were observed in five of five females in the 125 mg/kg bw/d recovery group. At the termination of the dosing period, relative liver weight was increased in the 25 mg/kg bw/d group. Absolute and relative liver weights were increased in the 125 mg/kg bw/d group (females). At the termination of the recovery period, the relative liver and ovary weights were significantly increased in the 125 mg/kg bw/d group. Increased ALT and ALP activities were seen in male and female animals and increased total cholesterol in the female animals of the 125 mg/kg bw/d group. On necropsy enlargement of the liver in females and blackish discoloration of the glandular stomach were observed in males from 25 mg/kg and in females at 125 mg/kg bw/d. Submucosal edema in the glandular stomach in males and females, haemorrhage and necrosis of the fundic mucosa of the glandular stomach, decreased goblet cells in the colon and periportal hypertrophy	(Hita Laboratory, 2007) (study report)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
		of the hepatocytes in males and diffuse liver cell hypertrophy in (all five) females were observed in the 125 mg/bw group. Decreased iron pigments of the ameloblasts at maturation stage was observed in the incisor of two female rat of the 125 mg/kg bw/d group at the termination of dosage and in one female rat of the 125 mg/kg bw/d recovery group. An irregular alignment of the ameloblasts at maturation stage was observed in the incisor of three female rats in the 125 mg/kg bw/d recovery group. Decreased iron pigments of the ameloblasts at maturation stage was observed in the incisor of two female rat of the 125 mg/kg bw/d group at the termination of dosage and in one female rat of the 125 mg/kg bw/d recovery group. An irregular alignment of the ameloblasts at maturation stage was observed in the incisor of three female rats in the 125 mg/kg bw/d recovery group. In the recovery group, in addition to discoloured incisors, mottled teeth and decreased iron pigments of the ameloblasts at maturation stage observed during and the end of the dosing period, delamination of the low incisor tip surface, cell infiltration of the gingiva and irregular alignment of ameloblasts at maturation stage were newly observed. Changes in the stomach, intestinal tract and liver had disappeared or improved.	
90-day study According to US EPA OPPTS 870.3100 (1998), OECD TG 408 Reliability 2 Rats (Crl:CD(SD)) were approximately 7 to 8 weeks old at study start. 10 animals/sex/dose group Fluoride concentrations were determined in plasma and urine. No histopathology data on the trabecular bone (only decalcified	Oral study, 5, 25, 125 and 250 mg/kg bw/d and a vehicle control group. The substance was diluted in NANOpure water. All animals were dosed once daily by gavage at a dose volume of 5 mL/kg bw. All animals were treated for 90 days. Additional animals were assigned to recovery groups of 1 month (10 animals/sex/dose) and three month (5 animals/sex/dose). In compliance with GLP. The purity of 6:2 FTOH was 99.7 %.	Substance-related mortality was observed at 125 mg/kg bw/d (1/25 females at day 62) and 250 mg/kg bw/d (6/25 males and 13/25 females from days 22 to 84), with the majority of the deaths attributed to kidney degeneration and necrosis. Following 90 days of dosing, effects on organ weights were present in the testes, liver and kidney of males and in livers and kidneys of females. No effects on organ weights were observed at 5 mg/kg/day in males or females. Relative testes weight was increased in males at all test doses. Relative liver and kidney weight parameters were increased in male rats dosed with 25, 125, and 250 mg/kg/day and in female rats dosed with 125 mg/kg/day and in the single female rat remaining at 250 mg/kg/day. Following a one-month recovery, male and female rats at the highest dose had increased liver weights, whereas no increases over control rats were observed following 3 months of recovery. In addition, thyroid weights in female rats were increased in the 250 mg/kg/day group at the 1-month recovery time point and in the 25, 125, and 250 mg/kg/day groups at the 3-month recovery time point. Dental effects included whitened teeth and increased incidence in missing/broken/misaligned incisors in the 125 mg/kg bw/d and 250 mg/kg bw/d group. Histopathological investigations showed an effect on the ameloblastic epithelium of the teeth in male rats at 250 mg/kg bw/d. These findings were present at the 1-month recovery sacrifice (250 mg/kg bw/d both sexes), but had resolved by the 3-month recovery sacrifice.	(Charles River Laboratories Preclinical Services, 2012) (study report) Cited in (Serex et al., 2014) (publication)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
bone medullary cavity examined)		Plasma fluoride concentrations increased from 0.1 mg/L in control animals (both sexes) and 5 mg/kg bw/d group (both sexes) and 25 mg/kg bw/d group (females only) to 0.2 mg/L in 25 mg/kg bw/d group (males only). At 125 mg/kg bw/d the plasma fluoride concentration yielded 0.7 mg/L in males and 0.6 mg/L in females. At 250 mg/kg bw/d the plasma fluoride concentration yielded 0.9 mg/L in males (mean of 9 animals) and to single value of 1.1 mg/L in the only surviving female rat. Urine fluoride was increased in all treated male and female groups, dose-relationship at 5 and 25 mg/kg/d was less clear for females. Liver effects of minimal severity were observed at the end of dosing in females at 25 mg/kg/day and above and in male rats at 125 mg/kg/day and above. These effects included single-cell necrosis, vacuolization, oval/biliary hyperplasia, hepatocellular hypertrophy and periportal inflammation. 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 rats (125 and 250 mg/kg/day females) had biliary hyperplasia. At 3 months recovery, all doses (5, 25 125 and 250 mg/kg bw/d) were investigated by histopathology.	
Subacute Inhalation Toxicity: 28 d study According to OECD TG 412 Reliability 2 Rat, Crl:CD (SD) 8 weeks old at study start 20/ sex/group (control; high dose), 10 males and females used for recovery group, 10/sex/group (low-dose; mid-dose)	Inhalation study (vapour, whole body), 0, 1, 10, 100 ppm The substance was formulated in a vehicle of corn oil 6 hours/day, 5 day/week, 23 exposures over a 4-week period In compliance with GLP. The purity of 6:2 FTOH was 99.94 %.	No effect on body weight, food consumption, clinical signs of toxicity 100 ppm (1.49 mg/l): decreased motor activity in males during 4th week of exposure (rerversible during recovery period); increased absolute liver weights; clinical chemistry: increased mean serum bilirubin levels, increased ALT in females; microscopic findings: increased lamination of dentin of the incisor teeth and incomplete decalcification of enamel of the incisors and the bone trabeculae in tibia and femur, but no histopathological effects observed	(DuPont Haskell Global Centers for Health & Environmental Sciences, 2011) (study report)
According to OECD TG 415. Reliability 2 Sprague-Dawley rats (Crl:CD(SD)), were	Oral study, 5, 25, 125 and 250 mg/kg bw/d and a vehicle control group. The substance was formulated in a vehicle of 0.5 % aqueous	In the parental generation rats some unscheduled deaths occurred at 125 and 250 mg/kg bw/d. At 250 mg/kg bw/d, three male rats and 13 female rats were found dead or were humanely euthanized due to adverse clinical signs during the dosage period. For the males, deaths occurred between test days 76 and 81. For females, the deaths occurred throughout all phases of the dosing period, beginning on test day 23. During premating dosing four females died, during gestation	(Charles River Laboratories, 2008) (study report) Cited in (O'Connor et

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
approximately 7 weeks old at study start. 20 animals/sex/dose group No data on fluoride concentrations in plasma, urine, dentin or bone matrix. No histopathology data on the trabecular bone (only decalcified bone medullary cavity examined).	methylcellulose. All animals were dosed once daily by gavage at a dose volume of 5 mL/kg bw. Male and female rats were dosed for at least 70 days prior to mating, and throughout the cohabitation period (ca 2 weeks), gestation (females only), and lactation (females only). Offspring from the first generation were not directly dosed. In compliance with GLP. The purity of 6:2 FTOH was 99.7 %.	period five females died and finally, during lactation period four females died. In the 125 mg/kg bw/d group, three male rats were found dead. Deaths occurred between test days 76 and 86. Test substance-related effects on the teeth were the most common clinical signs observed in parental male and female rats, and the incidence were statistically significantly higher at 125 and 250 mg/kg bw/d. The most common findings were increased incidences of whitened teeth, missing teeth, misaligned or broken teeth, and overgrown incisors. These effects were observed throughout the dosing periods for males, typically with the first occurrences late in the premating period. The effects on the teeth in females were more frequently observed in gestating and lactating dams, most likely due to the increased duration of test substance administration. The pups of the first generation were investigated at day 22 post-partum. No macroscopic effects were reported on the teeth of the offspring.	al., 2014) (publication)
According to OECD TG 415 and US EPA, OPPTS 870.3550. Reliability 2 Mice, Crl:CD1(ICR). Male mice were 50 days old at study start. Female mice were 75 days old at study start. 15 animals/sex/dose group Liver, nose/teeth, ovaries, uterus, vagina, and mammary gland were examined microscopically in all dose levels of parental	Oral study, 1, 5, 25 and 100 mg/kg bw/d and a vehicle control group. The substance was formulated in a vehicle of 0.1 % Tween-80 in 0.5 % aqueous methylcellulose. All animals were dosed once daily by gavage at a dose volume of 5 mL/kg bw. Male mice were dosed for 70 days prior to mating and throughout the cohabitation period (ca 2 weeks). Female Mice were dosed for 14 days prior to mating, and throughout the cohabitation period, gestation, and	One male and two female mice at 100 mg/kg bw/d were found dead or humanely euthanized during the premating of gestation periods. During the lactation period, females administered 100 mg/kg bw/d exhibited statistically significantly lower body weight gain, food consumption, and food efficiency during the intervals (lactation day) LD 0-7 and LD 7-14, compared with controls, resulting in statistically significantly lower body weight on LD 7 and LD 14. There were no effects in females at dose levels ≤ 25 mg/kg bw/d. Organ weight effects were observed in liver and kidney of males and females at 100 mg/kg bw/d with statistically significantly increased relative organ weights. In males the relative testes weight was statistically significantly increased at 100 mg/kg bw/d and in females the relative uterus weight was statistically significantly increased at 100 mg/kg bw/d. Microscopic findings indicative of toxic effects on the liver were present in males and females at 100 mg/kg bw/d and in low incidences in females at 25 mg/kg bw/d. These changes were generally more severe in females and included hepatocellular hypertrophy, oval cell hyperplasia, single cell necrosis of hepatocytes, and cystic degeneration (females only). Minimal microscopic hepatocellular hypertrophy was also present in males at 5 and 25 mg/kg bw/d and in females at 5 mg/kg bw/d. Substance-related changes in the incisor teeth, consistent with	(DuPont Haskell Global Centers for Health & Environmental Sciences, 2013) (study report) Cited in (Mukerji et al., 2015) (publication)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
animals.	lactation. In compliance with GLP. The purity of 6:2 FTOH was 99.7 %.	fluoride exposure, were present in males and females at 100 mg/kg bw/d. These changes included degeneration and atrophy of ameloblastic epithelium, accentuation of the normal laminar pattern of dentin and an increase in observed incomplete decalcification of enamel and/or dentin. Degeneration and atrophy of ameloblasts was characterized by segmental disorganization and attenuation of ameloblastic epithelium of the incisor teeth. Lamination of dentin was characterized by the presence of concentric basophilic rings within the dentin of these teeth. There were no adverse changes in the teeth of males or females at dose levels ≤ 25 mg/kg bw/d. Incomplete decalcification of nasal bone was observed in some animals at the 100 mg/kg bw/d dose level.	
Combined Repeated Dose Toxicity Study with Reproduction/ Developmental Screening Test According to OECD TG 422 Reliability 2 Rat, Crl:CD (SD) 10 weeks old at study start 15/ sex/group (control; high dose), 5 animals used for recovery group, 10/sex/group (low-dose; mid-dose)	Oral study, 0, 25, 75, 225 mg/kg bw The substance was formulated in a vehicle of corn oil Rats were dosed for 14 days prior to mating; males until day prior to euthanasia; females through LD3 In compliance with GLP. The purity of 6:2 FTOH was 98.52 %.	225 mg/kg bw: mortalities (1/15 males, 11/15 females) related to tubular lesions in kidneys, necrosis of adrenal cortex, bone marrow depletion; clinical findings include emaciation, hypoactivity, unkempt appearance, body cool to touch and labored respiration; serum chemistry parameters: in females increased urea nitrogen, creatinine, potassium bilirubin, AST and ALT, total protein and globulin, decrease in sodium and chloride and increased albumin in males and females; higher liver weight and hepatic centrilobular hypertrophy in males; tubular degeneration, dilatation and vacuolation in kidneys in males and females (associated with pale kidneys and higher kidney weight), changes in adrenal cortex and bone marrow Reproductive performance and gestation length unaffected; dystocia in 1 female; high pup mortality and lower pup weights observed but litter data confounded by high dam mortality 75 mg/kg bw: effects on body weight and body weight gain	(WIL Research Laboratories, 2005)
Prenatal Developmental Toxicity Study According to OECD TG 414 Reliability 2 Rat, Crl:CD (SD) 67 days old at study start 22 time-mated females/group	Oral study, 0, 5, 25, 125, 250 mg/kg bw The substance was formulated in a vehicle of 0.5 % aqueous methylcellulose. All animals were dosed once daily by gavage at a dose volume of 5 mL/kg bw. Daily gavage GD 6-20	Dams: no mortalities observed, at 250 mg/kg bw slight increase in incidence of stained or wet fur reduced mean daily food consumption and final mean body weight (10 % lower than control); no effects on reproductive outcome; no test substance-related maternal gross post-mortem observations reported Fetal alterations at 125 and 250 mg/kg bw: incomplete ossification of skull bones and wavy and/or thickened ribs (not statistically significant), at 250 mg/kg bw incidence of delayed pelvic bone ossification increased Dams examined grossly for external and internal alterations	(DuPont Haskell Global Centers for Health and Environmental Sciences, 2008) (study report) Cited in (O'Connor et al., 2014) (publication)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
	In compliance with GLP. The purity of 6:2 FTOH was 99.7 %.		

Table 8: Summary table of human data on STOT RE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
There are no human data available.				

Table 9: Summary table of other studies relevant for STOT RE.

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
There are no other studies available with relevance for STOT RE				

10.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Four repeated dose oral toxicity studies in rats (three studies) and mice (one study) showed substance-related effects on the teeth of the animals. All studies were performed in accordance with the appropriate guidelines. In the subacute study (Hita Laboratory, 2007) discoloration of the incisors, mottled teeth and delamination of the low incisor tip surface were observed in male and female rats treated with 125 mg/kg bw/d. Even if the discoloration of the incisors may be judged as less severe, mottled teeth and delamination of the low incisor tip surface have serious consequences for the stability of the teeth as shown in the studies with a longer exposure. In this 28-day study discoloration (2/5 males, 3/5 females) and mottled teeth (1/5 male) were already seen at 25 mg/kg bw/d. No recovery of teeth effects was seen at the end of the 1-month or 3-month recovery period (data available for the high dose only).

The one generation reproductive toxicity study in mice had two exposure scenarios (Mukerji et al., 2015): Male mice were exposed for 70 day prior to mating and throughout the cohabitation period of 14 day yielding a total exposure of 84 day. Female mice were exposed 14 day prior to mating, throughout the cohabitation period of 14 day, throughout gestation (18 days) and throughout lactation (21 days) yielding a total exposure of 67 days. Effects on the teeth were observed in males and females of the 100 mg/kg bw/d group. These effects included degeneration and atrophy of ameloblastic epithelium. Since this epithelium forms the enamel of the tooth, a degeneration and atrophy is judged as severe effect.

The one generation reproductive toxicity study in rats showed severe effects such as missing or broken teeth at a dosage of 125 mg/kg bw/d and higher (O'Connor et al., 2014).

Dose-related increase of mortalities with delayed occurrence were seen at 125 mg/kg bw/d (day 62) and at 250 mg/kg bw/d that together with mortalities (for males, death occurred between test days 76 and 81, for females, the deaths occurred throughout all phases of the dosing period) seen in the one-generation study supports the need for classification.

Furthermore, a subacute inhalation study (DuPont Haskell Global Centers for Health & Environmental Sciences, 2011) showed effects on teeth such as increased lamination of dentin and incomplete

decalcification of enamel of the incisors at 100 ppm (1.49 mg/l) when the whole body of rats was exposed to vapour for 6 hours/day. However, these effects did not include histopathological changes of teeth. As effects are less severe than effects observed in the oral studies, they are considered as supportive evidence.

In contrast, in a combined repeated dose toxicity study with reproduction/developmental screening test and in a prenatal developmental toxicity study no effects on teeth were reported (DuPont Haskell Global Centers for Health and Environmental Sciences, 2008; WIL Research Laboratories, 2005). However, it is not clear from the results reported if teeth were analysed in detail.

Table 10: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days [if adequate, otherwise please delete]

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
(Hita Laboratory, 2007)	25	28 days	8	STOT RE 1 (≤ 10 mg/kg bw/d guidance value)
(Serex et al., 2014)	125	90 days	125	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)
(O'Connor et al., 2014)	125	At least 84 days	117	None (≤ 100 mg/kg bw/d guidance value)
(Mukerji et al., 2015)	100	At least 84 days in males At least 67 days in females	93.3 74.4	STOT RE 2 (≤ 100 mg/kg bw/d guidance value) STOT RE 2 (≤ 100 mg/kg bw/d guidance value)

The subchronic oral toxicity study in rats showed severe effects such as missing or broken teeth at a dosage of 125 mg/kg bw/d and higher (Serex et al., 2014). Measurements of fluoride in the plasma showed a treatment related increase from 0.1 mg/L to 0.2 mg/l in male rats at 25 mg/kg bw/d and to 0.6 (females) mg/L and 0.7 (males) mg/L in the 125 mg/kg bw/d group. Increased urine fluoride concentrations were seen in all treated male and female groups (with less clear dose-relationship for the female groups). The fluoride release from 6:2 FTOH is the most likely mode of action of the damage to the teeth.

A review emphasized the suitability of small rodents as a model for the study of human dental fluorosis (Bronckers et al., 2009).

The enamel is a target of the fluoride action. The molecular mechanism underlying enamel fluorosis is still unknown (Lyaruu et al., 2014). Enamel formation by ameloblasts is a 2-step-event. First, secretory ameloblasts synthesize and secrete a matrix rich in amelogenins, in which long thin crystal ribbons are formed. In the maturation stage, most of the matrix is removed and the crystals expand. Maturation ameloblasts have ion-transporting, resorptive, and degrading functions and cyclically transform into 1 of 2 morphologically distinct cell types; ruffle-ended or smooth-ended ameloblasts (Lyaruu et al., 2014).

Fluoride interacts with the function of ameloblasts at all stages of the development of ameloblasts. Fluoride reduces degradation of matrix proteins by lowering the output of proteases by the ameloblasts. Fluoride acts directly on protease activity in the extracellular matrix and inhibits matrix degeneration. Fluoride changes the adsorption characteristics, surface area, or surface properties of enamel crystals to which matrix proteins

adhere. Fluoride reduces calcium in the enamel fluid required for protease activity. Fluoride impairs endocytosis and intracellular degradation of matrix by modulating ameloblasts. Fluoride increases apoptosis or stimulates some of the maturation ameloblasts to migrate from the ameloblastic layer (Bronckers et al., 2009).

The improper mineralization that occurs with enamel fluorosis is thought to be due to inhibition of the matrix proteinases responsible for removing amelogenin fragments. The delay in removal impairs crystal growth and makes the enamel more porous. The degree of porosity of such teeth results in a diminished physical strength of the enamel, and parts of the superficial enamel may break away (National Research Council, 2006).

EFSA used the effects on dental fluorosis to define Tolerable Upper Intake Level for fluoride for children up to the age of eight years. EFSA also review the effects on bones (skeletal fluorosis). The observed teeth effects at increased plasma and urine levels of fluoride appears similar to chronic fluorosis in humans where chronic high intake of fluoride may lead to dental fluorosis and skeletal fluorosis that is likely to result in increased fracture rates in the population. Ninety-nine percent of the total fluoride content of the body is concentrated in calcified tissue, bone and teeth (EFSA NDA Panel, 2013).

Therefore, bones and teeth are important targets of fluoride toxicity. The mechanism is described as follows. Because of similarities in size and charge, fluoride readily replaces OH- in the crystal lattice structure by an exchange and adsorption reaction. When the content of fluoride in bone reaches 2500 ppm, major pathological changes begin to occur. Mottled osteons appear, characterised by hypomineralisation, enlarged peripheral osteocyte lacunae, tangled canaliculi and increased numbers of pheripheral osterocytes with loss of osteocytes in the remainder of the osteon. Excessive fluoridation reduces the biomechanical properties of the bone, increases resorption and remodelling activities (which is observed as enlargement of the marrow cavity), converts the inner cortex to cancellous bone, and accelerates the development of resorption cavities in the outer cortical laminar zone (Woodard et al., 2002). As pointed out above, these effects on the bones may result in increased fracture rates in the population.

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.

10.10.2 Comparison with the CLP criteria

Four repeated dose toxicity studies in rats (three studies) and mice (one study) showed consistently substance-related adverse effects on the teeth of the animals. The extrapolated effective doses of two of these studies were within the guidance value range of STOT RE 1 or STOT RE 2 (see Table 10). In the subacute (Hita Laboratory, 2007) mottled teeth and delamination of the low incisor tip surface were observed in male and female rats treated from doses of 25 mg/kg bw/d onwards. Mottled teeth and delamination of the low incisor tip surface have serious consequences for the stability of the teeth as shown in the studies with a longer exposure and fulfil the criteria of point 3.9.2.7.3 d) “significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination”.

The one generation reproductive toxicity study in mice had two exposure scenarios (Mukerji et al., 2015): Effects on the teeth were observed in males and females of the 100 mg/kg bw/d group. These effects included degeneration and atrophy of ameloblastic epithelium. Since this epithelium forms the enamel of the tooth, a degeneration and atrophy is judged as severe effect und fulfils the criteria of point 3.9.2.7.3 d) “significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination”.

Two other studies showed serious effects such as missing or broken teeth but these effects were observed at doses beyond the guidance values of 100 mg/kg bw/d. However, these effects confirm the severity of the effects observed at doses below 100 mg/kg bw/d. The effective dose levels of the studies (O'Connor et al., 2014; Serex et al., 2014) were formally slightly above the guidance value, however indications on (urine/plasma) fluorosis were seen starting at low doses of 25 mg/kg bw/d ((Serex et al., 2014), no such data

in (O'Connor et al., 2014)). Delayed mortalities at ≥ 125 mg/kg bw/d (O'Connor et al., 2014) were considered as findings supporting the classification proposal.

STOT RE 2 is preferred on a weight of evidence that takes into consideration the available data.

10.10.3 Conclusion on classification and labelling for STOT RE

Two studies showed serious effects on teeth and fulfil the criteria of point 3.9.2.7.3 d) "significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination". The effects were mottled teeth and delamination of the low incisor tip surface in one study with an extrapolated effective dose of 8 mg/kg bw/d and degeneration and atrophy of ameloblastic epithelium in the second study with an extrapolated effective dose of 74 mg/kg bw/d. These values are either within the range for guidance values for STOT RE 2 ($10 \leq C \leq 100$ mg/kg bw/d) or even in the range for guidance values for STOT RE 1 ($C \leq 10$ mg/kg bw/d) after oral exposure. By weight of evidence taking into account all available studies which consistently indicated treatment-related chronic fluorosis-related tooth abnormalities it is proposed that 6:2 FTOH should be classified and labelled as STOT RE 2, H371 (May cause damage to organs (skeletal system) through prolonged or repeated exposure).

10.11 Aspiration hazard

This endpoint is not addressed in this CLH report and is outside the scope of the public consultation.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 11: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
OECD TG 301 D	5 % biodegradation (test material analysis) after 28 days; average of three replicates	Reliability 4 (secondary literature); poor documentation in registration dossier (Registrant: reliability 2)	Registration dossier (Kurume Laboratory, 2010)
OECD TG 301 B	21 % CO_2 evolution after 28 days (replicate 1) 0 % CO_2 evolution after 28 days (replicate 2)	Reliability 3; not valid (difference of replicates > 20 %) (registrant: reliability 1)	Registration dossier (Dr. U. Noack-Laboratorium, 2000)
Soil (flow through system)	DT50= 1.3 days (primary degradation) Transformation products: 5:3 polyfluorinated acid, perfluorohexanoic acid, perfluoropentanoic acid, perfluorobutanoic acid 5:2 sFTOH	Reliability 2	(Liu et al., 2010a).
Soil (closed system)	DT50= 1.6 days (primary degradation) Transformation products: 5:3 polyfluorinated acid, perfluorohexanoic acid, perfluoropentanoic acid, perfluorobutanoic acid,	Reliability 2 (registrant: reliability 2)	(Liu et al., 2010b)

Method	Results	Remarks	Reference
	4:3 polyfluorinated acid, 5:2 sFTOH		
River sediment system	DT50= 1.8 days (primary degradation) Transformation products: 5:3 polyfluorinated acid, perfluorohexanoic acid, perfluoropentanoic acid, perfluorobutanoic acid, 4:3 polyfluorinated acid, 5:2 sFTOH	Reliability 2 (registrant: reliability 2)	(Zhao et al., 2013)

11.1.1 Ready biodegradability

The ready biodegradability of 6:2 FTOH was evaluated in a closed bottle test (OECD TG 301 D). The initial concentration of 6:2 FTOH used in this study was 100 mg/L (test material). Activated sludge was used as inoculum. After 28 days, an average biodegradation of 5 % (average of three replicates) was determined. Further details on inoculum as well as test conditions were not given in the registration dossier. Upon request, the study report could not be made available to the dossier submitter.

Furthermore, a test according to OECD TG 301 B (CO_2 Evolution Test) was performed. 40 mg/L of the test material was used as initial concentration. Domestic activated sludge was used as inoculum. Further details on the study are not published. After 28 days, 21 % CO_2 evolution and 0 % CO2 evolution were observed in two replicates. The difference of the biodegradation values of the two replicates is > 20 %, therefore, the study should be considered as not valid. In addition, the test method according to OECD TG 301 B is not suitable for volatile test substances.

11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

No data available.

11.1.4 Other convincing scientific evidence

No data available.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

Not relevant for C & L.

11.1.4.2 Inherent and enhanced ready biodegradability tests

The biodegradability of 6:2 FTOH (2.8 µg/ml and 20 µg/ml) was investigated with a mixed aerobic bacterial culture developed from activated sludge from an industrial wastewater treatment plant (Registration dossier, (Liu et al., 2010b)). The sludge was previously exposed to fluorinated chemicals. The concentration of 6:2 FTOH decreased to 1.6-2.8 % after 7 days (primary biodegradation). Metabolite concentrations reached steady state after 14-28 days (metabolites: 6:2 fluorotelomer unsaturated acid, 5:2 secondary alcohol (5:2 sFTOH), 6:2 fluorotelomer saturated acid; 5:3 polyfluorinated acid, perfluorohexanoic acid, perfluorobutanoic acid and perfluoropentanoic acid). Adsorption of the transient metabolites to rubber septa cannot be excluded. Due to the adaption of the inoculum the study should not be used for classification and labelling purposes.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

The aerobic biodegradation of 6:2 FTOH was performed in a flow through soil incubation system (Liu et al., 2010a). After 1.3 days, 50 % of ^{14}C labelled 6:2 FTOH disappeared from soil, because of microbial degradation and volatilisation. The overall mass balance during the 84-day incubation averaged 77 % and 87 % for the live and sterile treatments, respectively. 16 % [^{14}C] 5:2 sFTOH, 14 % [^{14}C] 6:2 FTOH and 6 % [^{14}C] CO_2 were measured in the airflow after 84 days. In soil, the following stable transformation products were detected after 84 days: 5:3 polyfluorinated acid (12 %), perfluorohexanoic acid (4.5 %), perfluoropentanoic acid (4.2 %), and perfluorobutanoic acid (0.8 %). In soil-bound residues, the major transformation product was 5:3 polyfluorinated acid, which may not be available for further biodegradation in soil. In a further study, the authors investigated the aerobic biodegradation of 6:2 FTOH (without ^{14}C-labelling) in soil (closed system) (Liu et al., 2010b). 6:2 FTOH primary degradation half-life was 1.6 days. After the rapid decline of 6:2 FTOH the concentration leveled-off after 28 days. The overall mass balance in aerobic soil was ~67 % after 180 days (e.g. due to irreversible bond to soil). After 180 days the following substances were accounted: 30 % perfluoropentanoic acid, 8.1 % perfluorohexanoic acid, 1.8 % perfluorobutanoic acid, 15 % 5:3 polyfluorinated acid, 1 % 4:3 polyfluorinated acid, 3 % 6:2 FTOH, and 7.1 % 5:2 sFTOH.

In an aerobic river sediment system similar biotransformation products as in soil were detected (Zhao et al., 2013). The recovery of 6:2 FTOH and quantifiable transformation products ranged 71-88 mol% of initially applied 6:2 FTOH. The lower mass balance compared to sterile control (86-98 mol%) could be explained by formation of bound residues. The 6:2 FTOH primary degradation half-life in sediment system was estimated to be 1.8 days. After the initially rapid decrease, the 6:2 FTOH concentration was relatively constant after day 28. After 100 days 22.4 mol% 5:3 polyfluorinated acid, 20.2 mol% 5:2 sFTOH, 10.4 mol% perfluoropentanoic acid, 8.4 mol% perfluorohexanoic acid, 1.5 mol% perfluorobutanoic acid and 2.7 mol% 4:3 polyfluorinated acid were detected.

11.1.4.4 Photochemical degradation

Ellis and co-workers studied the kinetics of the reactions of Cl atoms and OH radicals with a series of fluorotelomer alcohols with differing chain lengths (4:2; 6:2, 8:2 FTOH) in 700 Torr of N2 or air, diluent at 296 +/- 2K. Interestingly, the length of the perfluorinated carbon chain residue had no discernible impact on the reactivity of the molecules. The authors conclude an atmospheric life-time of the FTOHs of 20 days by reaction with OH radicals (Ellis et al., 2003).

The photooxidation of 6:2 FTOH was investigated at the surface of TiO_2, SiO_2, Fe_2O_3, Mauritanian sand, and Icelandic volcanic ash (Styler et al., 2013). At all surfaces the photooxidation resulted in the production of surface-sorbed perfluoroalkyl carboxylic acids (PFCAs) like perfluorohexanoic acid, perfluorobutanoic acid and perfluoropentanoic acid. These results provide evidence that the heterogeneous photooxidation of FTOHs at metal-rich atmospheric surface may provide a significant loss mechanism for FTOHs and also act as a source of aerosol-phase PFCAs close to source regions. The long-range transport of these aerosols is a possible source of PFCAs to remote areas.

11.1.5 Conclusion on rapid degradation

The available information on ready biodegradability of 6:2 FTOH does no demonstrate that the substance is readily biodegradable.

A rapid primary degradation was observed for 6:2 FTOH in aquatic sediment and soil (half-life < 16 days). Nevertheless, based on the ECHA Guidance on the Application of the CLP criteria (Annex II), these data can only be used if it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. A hazard to the aquatic environment cannot be excluded as not for all transformation products sufficient data are available.

Since there is no clear evidence of rapid degradation (only primary degradation), 6:2 FTOH should be considered as not rapidly degradable according to CLP-criteria.

11.2 Environmental fate and other relevant information

The adsorption coefficient was investigated according to OECD TG 106 (analysis by LC/MS/MS). Three soils with organic carbon content of 0.52 to 8.18 and six initial test concentrations between 0.3 and 3.0 mg/L were used. A log Koc of 2.43 was determined at 22.5 °C using Freundlich sorption model (Liu and Lee, 2007).

11.3 Bioaccumulation

Table 12: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
OECD TG 107	Log Pow = 4.54	Reliability 2 (registrant: reliability 2)	Registration dossier (Carmosini and Lee, 2008)
OECD TG 305	BCF ≤ 36 (1 µg/L) BCF = 46 (10 µg/L)	Reliability 2 (registrant: reliability 2)	Registration dossier (Kurume Laboratory, 2002)
OECD TG 305	BCF = 24 - 99 (1 µg/L) BCF = 8.4 - 58 (10 µg/L)	Reliability 2 (registrant: reliability 2)	Registration dossier (Kurume Laboratory, 2007)

11.3.1 Estimated bioaccumulation

No data available.

11.3.2 Measured partition coefficient and bioaccumulation test data

A log Kow of 4.54 was determined according to OECD Guideline 107 (temperature and pH not provided in registration dossier). A concentration of 1740 mg/L was made with the test substance and purified octanol. The test substance/octanol solution was equilibrated with varying volumes of high purity water in 9 mL glass centrifuge tubes for 24 hours and one week. After equilibration, three to five aliquots were taken from both the aqueous and octanol phases of each tube, diluted with methanol and analysed by LC/MS/MS (Registration dossier Carmonsini and Lee, 2008).

A fish bioconcentration test according to OECD TG 305 was conducted for 28 days on *Cyprinus carpio* with two exposure levels (1 and 10 µg/L nominal; 0.835 and 9.11 µg/L measured) of the test substance (registration dossier Kurume, 2002). The test temperature ranged from 24.6 to 25.9°C and the pH from 7.6 to 7.9. The lipid content was 2.9 5 % at the start of the exposure and 2.26 % at the end of the exposure. After 28 days whole body w.w. BCF values of ≤ 36 (exposure level 1 µg/L) and 46 (exposure level 10 µg/L) were determined (steady state).

A further bioconcentration test according to OECD TG 305 (deviation: no post-exposure (depuration) phase) was conducted for 28 days on Cyprinus carpio with two exposure levels (1 and 10 µg/L nominal) of the test substance (registration dossier Kurume, 2007). After 28 days whole body w.w. BCF values of 24 - 99 (exposure level 1 µg/L) and 8.4 - 58 (exposure level 10 µg/L) were determined.

The determined BCF-values are below the CLP trigger value of 500. However, the derived Log Kow value meets the CLP trigger value for indication of bioaccumulation (Log Kow ≥4). Following the CLP regulation (section 4.1.2.8.1), the available, reliable experimental BCF determined in fish is taken in preference to the Log Kow. Therefore, 6:2 FTOH has a low potential for bioaccumulation in the aquatic environment.

11.4 Acute aquatic hazard

Table 13: Summary of relevant information on acute aquatic toxicity

Method	Species	Results[1]	Remarks	Reference
OECD 203	*Pimephales promelas*	**96h-LC_{50}= 4.84 mg/L (mean measured)**	Reliability 1 (registrant: reliability 1)	Anonymous 1, 2007

OECD 203	*Oncorhynchus mykiss*	96h-LC_{50}= 9 mg/L (nominal)	Reliability 4 (registrant: reliability 1), not enough details	Anonymous 2, 2005
OECD 203	*Oryzias latipes*	96h-LC_{50}= 5.78 mg/L (mean measured)	Reliability 4 (registrant: reliability 2), not enough details	Anonymous 3, 2007
OECD 202	*Daphnia magna*	**48h-EC_{50}= 7.84 mg/L (mean measured)**	Reliability 1 (registrant: reliability 1)	(ECHA Registration dossier: DuPont Haskell Global Centers for Health & Environmental Sciences, 2007)
OECD 202	*Daphnia magna*	48h-EC_{50}= 8.3 mg/L (nominal)	Reliability 4 (registrant: reliability 1), not enough details	(ECHA Registration dossier: Safepharm Laboratories Ltd., UK, 2005)
OECD 202	*Daphnia magna*	48h-EC_{50}= 8.2 mg/L (mean measured)	Reliability 4 (registrant: reliability 2), not enough details	(ECHA Registration dossier: Kurume Laboratory, Chemicals Evaluation and Research Institute, Japan, 2007)
OECD 201	*Pseudokirchneriella subcapitata*	**72h-E_rC_{50}= 14.8 mg/L (measured)**	Reliability 1 (registrant: reliability 1)	(ECHA Registration dossier: DuPont Haskell Global Centers for Health & Environmental Sciences, 2007)
OECD 201	*Desmodesmus subspicatus*	72h-E_rC_{50}= 7.8 mg/L (measured)	Reliability 4 (registrant: reliability 1), not enough details	(ECHA Registration dossier: Safepharm Laboratories Ltd., UK, 2005)
OECD 201	*Pseudokirchneriella subcapitata*	72h-E_rC_{50}> 5.19 mg/L (measured)	Reliability 4 (registrant: reliability 2), not enough details	(ECHA Registration dossier: Kurume Laboratory, Chemicals Evaluation and Research Institute, Japan, 2007)

[1] Test material: CAS 647-42-7; EC 211-477-1

11.4.1 Acute (short-term) toxicity to fish

Three studies for short-term toxicity to fish are available.

An 96-hour acute toxicity test with fathead minnow, *Pimephales promelas*, according to OECD TG 203 was conducted in a static test-type. The test concentrations were analytically monitored by LC/MS analysis (nominal test concentrations: 0, 1.0, 2.0, 4.0, 8.0, and 16.0 mg/L; mean measured: 0, 0.751, 1.61, 3.12, 7.52 and 16.4 mg/L). For the test 5 organisms per replicate and 2 replicates were used. The photoperiod was 16 hours light per day (light intensity: 126-710 lux). The test temperature ranged from 21.4 to 21.6 °C, the pH from 7.0 to 7.3 and the dissolved oxygen concentration from 5.4 to 8.5 mg/L. No control mortality or behavioural abnormalities occurred. The fish in the control had a standard length of 2.2 to 2.8 cm and a wet weight, blotted dry, of 0.140 to 0.304 g. The validity criteria were fulfilled. The test resulted in an 96h-LC_{50} of 4.84 mg/L (mean measured concentrations) and an 96h-LC_{100} of 7.52 mg/L (mean measured). At 3.12 mg/L (mean measured) and below no mortality occurred.

The second 96-hour acute toxicity test was conducted with *Oncorhynchus mykiss* according to OECD TG 203 in a semi-static test-type. The test concentrations were analytically monitored. The test concentrations

ranged from 1.3 to 13 mg/L (nominal). The validity criteria were fulfilled according to the registrant. The resulting 96h-LC_{50} was 9 mg/L (nominal). The reliability was difficult to access because of too little details provided in the registration dossier.

The third 96-hour acute toxicity study was conducted with ricefish, *Oryzias latipes*, according to OECD TG 203 in a semi-static test-type. The test concentrations were analytically monitored and ranged from 2 to 10 mg/L (measured). The validity criteria were fulfilled according to the registrant. The test resulted in an 96h-LC_{50} of 5.78 mg/L (mean measured concentrations) and an 96h-NOEC of 3.06 mg/L (mean measured).

The second and the third study were evaluated with Reliability score of 4 because in the registration dossier not enough details were provided to score them better.

11.4.2 Acute (short-term) toxicity to aquatic invertebrates

Three studies for short-term toxicity to aquatic invertebrates are available.

The first acute toxicity test with *Daphnia manga* was conducted according to OECD TG 202 under GLP with analytical monitoring (LC/MS/MS) in a static test-type. The test temperature ranged from 20.1 to 20.4 °C and the pH from 7.2 to 7.6. Nominal test concentrations were 0, 0.625, 1.25, 2.50, 5.00, and 10.0 mg/L and the mean measured concentrations were 0, 0.600, 1.23, 2.39, 4.90, and 9.29 mg/L. For the test system, 10 organisms were used per test vessel and two replicates per concentration. The photoperiod was 16 hours light per day (495-534 lux). The resulting 48h-EC_{50} (endpoint: immobility) was 7.84 mg/L and the 48h-NOEC was 2.39 mg/L based on mean measured concentrations. Lethargy was observed in surviving daphnids in the 2.39, 4.90, and 9.29 mg/L mean measured concentrations at the end of the study. The validity criteria were fulfilled.

The second acute toxicity test with *Daphnia manga* was conducted according to OECD TG 202 under GLP with analytical monitoring under static test conditions. The test concentrations ranged from 0.14 to 14 mg/L (nominal). The resulting 48h-EC_{50} (endpoint: immobility) was 8.3 mg/L and the 48h-NOEC was 2.5 mg/L based on nominal concentrations. According to the registrant, the validity criteria were fulfilled.

The third acute toxicity test with *Daphnia manga* was conducted according to OECD TG 202 with analytical monitoring in a static test-type. The test concentrations ranged from 1.30 to 15.5 mg/L (nominal). The resulting 48h-EC_{50} (endpoint: immobility) was 8.2 mg/L and the 48h-NOEC was 1.33 mg/L based on mean measured concentrations. According to the registrant, the validity criteria were fulfilled.

The second and the third study were evaluated with Reliability score of 4 because in the registration dossier not enough details were provided to score them better.

11.4.3 Acute (short-term) toxicity to algae or other aquatic plants

Three studies concerning the toxicity to aquatic algae and cyanobacteria are available.

The first toxicity study with *Pseudokirchneriella subcapitata* was conducted according to OECD TG 201 under GLP with analytical monitoring (LC/MS) in a static test-type. The test temperature ranged from 23.8 to 24.0 °C and the pH value from 7.97 to 9.97. Nominal test concentrations were 0.200, 0.640, 2.00, 6.60, and 21.0 mg/L and the mean measured concentrations were 0.154, 0.623, 2.22, 7.10, and 23.5 mg/L. Four replicates were used per concentration (3 for the test and 1 for analytical sampling). The photoperiod was 24 hours light per day (6670 to 6980 lux). The resulting 72h-E_rC_{50} was 14.8 mg/L (measured). The NOE_rC was 2.22 mg/L (measured). All validity criteria (cell counts increased in the blank control by at least a factor of 16 in 72 hours and the coefficient of variation of average specific growth rates during the whole test period (0-72 hr) in the blank control replicates did not exceed 7%) were fulfilled.

The second toxicity study with *Desmodesmus subspicatus* was conducted according to OECD TG 201 under GLP with analytical monitoring in a static test-type. Mean measured concentrations ranged from 1.13 to 13 mg/L (1.3, 2.3, 3.1, 6.7 and 13). The resulting 72h-E_rC_{50} was 7.8 mg/L (measured). The NOE_rC was 1.3 mg/L (measured). All validity criteria were fulfilled according to the registrant.

The third toxicity study with *Pseudokirchneriella subcapitata* was conducted according to OECD TG 201 with analytical monitoring in a static test-type. Mean measured concentrations ranged from 0.0966 to

9.45 mg/L. The resulting 72h-E_rC_{50} was greater than 5.19 mg/L (mean measured). The NOE_rC was 1.47 mg/L (measured). All validity criteria were fulfilled according to the registrant.

11.4.4 Acute (short-term) toxicity to other aquatic organisms

No data available.

11.5 Long-term aquatic hazard

Table 14: Summary of relevant information on chronic aquatic toxicity

Method	Species	Results[1]	Remarks	Reference
OECD 305	*Cyprinus carpio*	no abnormality in behaviour or appearance was noted	Test not suitable to evaluate long-term fish toxicity	Anonymous 5, 2007
OECD 211 EPA 797.1330	*Daphnia magna*	**21d-NOEC= 2.16 mg/L (mean measured**)	Reliability 1	(ECHA Registration dossier: DuPont Haskell Global Centers for Health & Environmental Sciences, 2007)
OECD 201	*Pseudokirchneriella subcapitata*	**72h-NOE_rC= 2.22 mg/L (measured)**	Reliability 1	(ECHA Registration dossier: DuPont Haskell Global Centers for Health & Environmental Sciences, 2007)
OECD 201	*Desmodesmus subspicatus*	72h-NOE_rC= 1.3 mg/L (measured)	Reliability 4 (registrant 1), not enough details	(ECHA Registration dossier: Safepharm Laboratories Ltd., UK, 2005)
OECD 201	*Pseudokirchneriella subcapitata*	72h-NOE_rC= 1.47 mg/L (measured)	Reliability 4 (registrant 2), not enough details	(ECHA Registration dossier: Kurume Laboratory, Chemicals Evaluation and Research Institute, Japan, 2007)

[1] Test material: CAS 647-42-7; EC 211-477-1

11.5.1 Chronic toxicity to fish

There is one long-term toxicity test to fish documented in the registration dossier. As the test is a bioaccumulation study not covering the sensitive life stages of the organism, this test is not suitable to assess the chronic toxicity to fish.

11.5.2 Chronic toxicity to aquatic invertebrates

One long-term toxicity test to the aquatic invertebrate Daphnia magna is available conducted according to OECD TG 211 under GLP with analytical monitoring (LC/MS/MS) in a semi-static test-type. The test temperature ranged from 20.6 to 21.6 °C, the pH value from 7.6 to 8.1 and the dissolved oxygen concentration from 5.4 to 9.0 µg/L. The nominal test concentrations amounted to 0, 0.65, 1.3, 2.5, 5, and 10 mg/L and the mean measured concentrations amounted to 0, 0.557, 1.11, 2.16, 4.46, and 8.57 mg/L. Two organisms per test vessel were used and the control was composed of 5 replicates. The number of replicates for the test concentrations was not described in the RSS but it would be likely that this replicate number was also used for the test concentrations. The photoperiod was 16 hours light per day (17-40 lux). The test resulted in a NOEC of 2.16 mg/L (based on mean measured concentrations) (basis for the effect: adult survival, total live young per female, total immobile young per surviving female and length and weight of surviving females at day 21). As 90 % of the adults in the control test solution survived at the end of the test and the sum of live young produced per surviving female adult in 21 days was 112 (and therefore ≥ 60) all validity criteria were fulfilled.

11.5.3 Chronic toxicity to algae or other aquatic plants

Three studies concerning the toxicity to aquatic algae and cyanobacteria are available. For study details please see section 11.4.3.

The first toxicity study with *Pseudokirchneriella subcapitata* resulted in a NOE_rC of 2.22 mg/L (measured).

The second toxicity study with *Desmodesmus subspicatus* resulted in a NOE_rC of 1.3 mg/L (measured).

The third toxicity study with *Pseudokirchneriella subcapitata* resulted in a NOE_rC of 1.47 mg/L (measured).

11.5.4 Chronic toxicity to other aquatic organisms

No data available.

11.6 Comparison with the CLP criteria

11.6.1 Acute aquatic hazard

The lowest valid EC50/LC50 for classification is 4.84 mg/L for the fish Pimephales promelas. Therefore, no Aquatic Acute classification is necessary.

Table 15: Comparison with criteria for acute aquatic hazards

	Criteria for acute environmental hazards	**6:2 FTOH**	**Conclusion**
Acute Aquatic Toxicity	Cat. 1: $LC_{50}/EC_{50}/ErC_{50} \leq 1$ mg/L	Fish: 96h-LC_{50}= 4.84 mg/L (m) (*Pimephales promelas*) Invertebrates: 48h-LC_{50}= 7.84 mg/L (m) (*Daphnia magna*) Algae: 72h-ErC_{50}= 14.8 mg/L (m) (*Pseudokirch. subcapitata*)	**No classification necessary**

11.6.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

For aquatic invertebrates and algae long-term toxicity studies are available. The most sensitive NOEC was obtained from the test with Daphnia magna, being 2.16 mg/L (based on measured concentration). The test with algae resulted in a NOEC in the same order of magnitude.

Table 16: Comparison with criteria for long-term aquatic hazards

	Criteria for environmental hazards	**6:2 FTOH**	**Conclusion**
Rapid Degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide) Primary degradation: half-life < 16 days (if degradation products do not fulfil criteria for classification as hazardous to the aquatic environment)	no data available not readily biodegradable half-life < 16 days (soil, aquatic sediment), but hazard to the aquatic environment cannot be excluded for all transformation products	**Not rapidly degradable**
Bioaccumulation	BCF ≥ 500	BCF ≤ 36 - 99	**Not bioaccumulative (low potential for bioconcentration**

			in the aquatic environment)
Aquatic Toxicity	Not rapidly degradable substances: Cat. 1: NOEC ≤ 0.1 mg/L Cat. 2: NOEC ≤ 1 mg/L (based on Table 4.1.0 (b) (i) of the CLP Regulation)	Fish: No appropriate long-term toxicity tests are available. Invertebrates: 21d NOEC= 2.16 mg/L (m) (*Daphnia magna*) Algae: 72h-NOE_rC= 2.22 mg/L (n.a.) (*Pseudokirchneriella subcaptiata*)	**Aquatic Chronic 2** *(based on fish-LC_{50})*
	<u>Surrogate approach in absence of appropriate chronic toxicity reference data</u> (based on Table 4.1.0 (b) (iii) of the CLP Regulation)<u>:</u> Not rapidly degradable substances and/or bioaccumulative substances: Cat. 1: E/LC_{50} ≤ 1 mg/L Cat. 2: E/LC_{50} > 1 to ≤ 10 mg/L Cat. 3: E/LC_{50} > 10 to ≤ 100 mg/L	Fish: 96h-LC_{50}= 4.84 mg/L (m) (*Pimephales promelas*)	

11.7 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

6:2 FTOH is not rapidly degradable and has a low potential for bioconcentration in the aquatic environment. Chronic toxicity data on aquatic invertebrates and algae do not require an aquatic chronic classification according to Table 4.1.0 (b) (i). As chronic data is available for aquatic invertebrates and algae, the surrogate approach based on Table 4.1.0 (b) (iii) is not applicable. For chronic fish toxicity assessment not appropriate toxicity reference data is available and therefore the surrogate approach is used. The most protective valid acute LC_{50} is 4.84 mg/L (measured concentration) for *Pimephales promelas*. According to Figure 4.1.1 of the CLP Regulation the aquatic chronic classification is based on the most stringent outcome of the two assessments according to Table 4.1.0 (b) (i) and (iii). This results in a classification of 6:2 FTOH as Aquatic Chronic 2, H411 (based on Table 4.1.0 (b) (iii) of the CLP Regulation.

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