CLH report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: 8:2 Fluorotelomer alcohol (8:2 FTOH)

EC Number: 211-648-0

CAS Number: 678-39-7

Submitted by: Climate and Pollution Agency, Norway

June 2010

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Substance Name: 8:2 Fluorotelomer alcohol (1H,1H, 2H, 2H-Perfluoro-1-decanol)

EC Number: 211-648-0

CAS number: 678-39-7

Registration number (s):

Purity: 99 %

Impurities: < 1%; 8:2 Fluorotelomer α-β unsaturated alcohol ($F(CF_2)_7CF=CHCH_2OH$)

Proposed classification based on Directive 67/548/EEC criteria:

Xn;R48/20/22 Danger of serious damage to health by prolonged exposure

Proposed classification based on CLP criteria:

STOT RE.2-H373 Causes damage to organs (liver) through prolonged or repeated exposure

Proposed labelling:

Directive 67/548/EEC: Class of danger: Harmful (Xn)

R48/22

CLP Regulation: Pictogram: GHS08, Signal word: Warning

Hazard statement codes: H373

Proposed specific concentration limits (if any): none

Proposed notes (if any): none

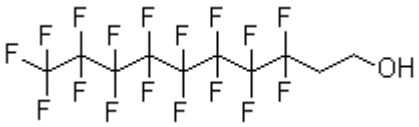
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	1H,1H,2H,2H-Perfluoro-1-decanol
	1,1,2,2-tetrahydroperfluoro-1-decanol,
EC Name:	1H,1H, 2H, 2H-Perfluorodecanol
CAS Number:	678-39-7
CAS name:	1-decanol,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro
IUPAC Name:	3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecan-1-ol,
	,

1.2 Composition of the substance

Chemical Name:	8:2 Fluorotelomer alcohol
EC Number:	211-648-0
CAS Number:	678-39-7
IUPAC Name:	3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecan-1-ol
Molecular Formula:	$C_{10}H_5F_{17}O$
	$F(CF_2)_8CH_2CH_2OH$
Structural Formula:	
Molecular Weight:	464.12
Typical concentration (% w/w):	99 %
Concentration range (% w/w):	97-99%

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Waxy solid	
VII, 7.2	Melting/freezing point	3.2	No information available	
VII, 7.3	Boiling point	3.3	No information available	
VII, 7.4	Relative density	3.4 density	No information available	
VII, 7.5	Vapour pressure	3.6	31 Pa at 25 ºC (Retention time method) 29 Pa at 45ºC (Headspace GC/AED method) 254 Pa ved 25 ºC , volatile, 99.9 % detected mainly in the gassousphase in the atmosphaere 0.227 kPa 0,023 mmHg	Vapour pressure seem sensitive to choice of method. Cobranchi et al 2006 Stock et al. 2004 Lei et al., 2004 Berti WR DuPont EMSE Report No 92-02
VII, 7.6	Surface tension	3.10	No information available	
VII, 7.7	Water solubility	3.8	1,4 x 10^{-4} g/l or 140 µg/l at 25 °C	Berti WR DPont EMSE Report No 92-02
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	No information available	
VII, 7.9	Flash point	3.11	No information available	
VII, 7.10	Flammability	3.13	No information available	
VII, 7.11	Explosive properties	3.14	No information available	
VII, 7.12	Self-ignition temperature		No information available	
VII, 7.13	Oxidising properties	3.15	No information available	
VII, 7.14	Granulometry	3.5	No information available	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No information available	
XI, 7.16	Dissociation constant	3.21	No information available	
XI, 7.17,	Viscosity	3.22	No information available	
	Auto flammability	3.12	No information available	
	Reactivity towards container material	3.18	No information available	
	Thermal stability	3.19	No information available	

	Stability degradation products row]		Stable at ambient room temperature	

2 MANUFACTURE AND USES

2.1 Manufacture

Manufacture of raw material for the synthesis of fluorotelomer-based surfactants and polymeric products.

2.2 Identified uses

8:2 FTOH is mainly used for coating of textiles, paper and carpets to achieve oil, stain and water repellent properties, cleaning agents and is present as residual raw materials (Dinglasan-Panlilio and Mabury, 2006). The reaction of fluorotelomer alcohol to make fluorotelomer acrylates or methacrylate esters leaves 0.1-0.5 wt% unreacted residual FTOH. The FTOHs are present in the ultimate sales products unless removed. A Norwegian study by Berger and Thomsen (Berger and Thomsen, 2006) showed that by extraction of a Norwegian "all weather coat" with ethylacetate and methanol there were measured nearly 1000 µg/m^2 8:2 FTOH and about 20 µg/m^2 PFOA.

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex IV of the CLP Regulation

8:2 Fluorotelomer alcohol is currently not included in Annex VI of the CLP Regulation.

3.2 Self classification(s)

8:2 Fluorotelomer alcohol is currently not self-classified.

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Oral:

Species	Dose (mg/kg)	Observations and Remarks	Ref.
Cr:CD® (SD) Rats	0, 5, 125 mg/kg bw 8-2 FTOH (99.2% purity with 0.8% 8-2 uFTOH ($C_8F_{17}CH=CHOH$) Gavage	Rats were exposed daily by oral gavage to 8-2 FTOH (0, 5 and 125 mg/kg bw) for 45 days, as a conditioning phase, to identify and obtain steady-state plasma kinetics, followed by a recovery period with sacrifice at day 53 to study kinetics and metabolism of 8-2 FTOH along with liver GSH status. Rats were sacrifice in groups of 3, first 3/sex of the unexposed group at day 0 followed by 3/sex/dose level at days 1, 8, 25 and 45. At day 46 after conditioning, 3/sex for the 5 and 125 mg 8-2 FTOH/kg bw groups were given radioactive 8-2 FTOH except from the control group (3/sex), after which they were sacrificed at day 53 to study ADME. The metabolites were quantitatively analyzed by LC-MS/MS, and a radiochromatographic method (liquid chromatography-accurate radioisotope counting LC-ARC) along with LC-MS and GC-MS methods. Liver GSH-status did not change during the experiment Most radioactive 8-2 FTOH was eliminated in the feces, relatively more at the higher dose. Elimination via urine was minor, and females eliminated more than males. The major metabolites in urine were PFOA, 7-2 sFTOH-gluc (females only) and 8-2 uFTOH-SCysNAcetyl (females only). The net systemic uptake of 8-2 FTOH was 3-1.5 fold higher in females than in males. In the liver PFOA, PFNA and 8-2 FTOH-sulf was detected in both sexes whereas 7-3 acid was detected in males only. In the kidney PFOA was detected in males only and 8-2 FTOHSulf in females only. In plasma 8-2 FTOHSulf was detected in females only. The maximum concentration of the parent 8-2 FTOH in plasma (C_{max}) was higher in female rats (271 ng/ml) than in male rats (88 ng/ml) at the high dose level. Independent of dose level, C_{max} for PFOA in plasma from male rats observed over the 45-day conditioning period at the low (1610 ng/ml) and high dose level (36,100 ng/ml) was much greater than in female rats at the low (102 ng/ml) and high dose levels (1673 ng/ml). C_{max} in liver for 8-2 FTOH was comparable for males and females at the low dose (309 vs. 202 ng/g, respectively) and high dose level	Fasano et al., 2009

		(5843 vs. 7590 ng/g, respectively). Independent of dose level, C_{max} for PFOA in liver of male rats observed over the 45-day conditioning period at the low (4033 ng/g) and high dose level (28,900 ng/g) were found to be much greater than the female rats (82 and 878 ng/g, low and high dose level, respectively). As was observed in plasma from control rats, the concentration of PFOA in liver from control males increased with time.	
Sprague-Dawley rats (Crl:CD (SD)IGS BR rats)	5 and 125 mg/kg 8:2 FTOH in Methylcellulose (0.5% wt/vol) Gavage	Single oral dose of 8:2 FTOH in females and males. The maximum concentration of 8:2 FTOH in plasma occurred at 1 h post dosing and cleared rapidly with a half-life of less than 5 h. The internal dose of 8:2 FTOH increased in a dose-dependent manner. At 7 days postdose, 4–7% of the administered radioactivity was present in tissues, and for the majority, 14C concentrations were greater than whole blood with the highest concentration in fat, liver, thyroid, and adrenals. The majority of 8:2 FTOH (>70%) was excreted in the faeces and 37-55% was identified as parent compound. Less than 4% was excreted in urine. About 1% of this was PFOA. Metabolites detected in the bile were principally composed of glucuronide and glutathione conjugates, 8:2 FTOH glucuronide conjugate, 8:2 uFTOH GSH conjugate and 8:2 FTUA GSH conjugate. Perfluorohexanoate (PFHxA) and perfluoroheptanoate (PFHpA) in addition to other metabolites was identified in excreta and plasma. The metabolism of 8:2 FTOH is proposed to occur by sequential removal of CF_2 groups.	Fasano et al. 2006
Sprague-Dawley rats (Crl:CD (SD)IGS BR rats)	0, 5, 25, 125 mg/kg/day 8:2 FTOH Gavage	Young adult male (10/group) and female (5/group) were exposed by oral gavage to 8:2 FTOH in an 84 day extended range-finding study to determine the length of time needed to reach a steady state blood fluorine level. Some animals (males and females) were allowed to recover for 75 days post-dosing. Total fluorine and 8:2 FTOH levels as well as levels of the metabolites 8:2 acid, PFOA and PFNA were measured. Steady state blood fluorine level was reached between day 60 and day 84. The plasma level of 8:2 FTOH did not exceed 0.074 ppm at steady state in neither males nor females. The plasma total fluorine level was 53 ppm (males) and 23 ppm (females) in the high dose groups, whereas the level of PFOA was 65.60 ppm and 1.85 ppm in the high dose group in males and females respectively. Thus, PFOA accounts for a large portion of the fluorine present in plasma in males, which was not the case for females following 84 days of 8:2 FTOH administration. In males, the highest concentration of PFOA was found in the liver at the lower doses and in plasma at the highest dose. Significant levels of PFOA were also found in kidneys. The levels of 8:2 acid and PFNA were low in the analysed tissues. The major metabolite in females was not identified in this study. The measurements of fluorinated compounds detected in plasma at steady state (day 84) showed that PFOA accounts for the majority of the fluorinated substances in males (85%) at 125 mg/kg /day. No information of the amount of 8:2 FTOH and PFNA in these samples were given.	Ladics, 2001

		However, the content of 8:2 FTOH, PFOA and PFNA was measured in males and females in various tissues at day 81 from the doses of 5, 25 and 125 mg/kg/day. There were major increases of PFOA in the liver, kidney and plasma and a slight increase in the fat. There was a slight increase of PFNA in the liver and kidney but no change in the fat levels. The level of 8:2 acid showed a slight increase in the fat and liver while the kidney levels were almost unchanged.	
Sprague-Dawley rats (S-D rats)	400 mg/kg of 8:2 FTOH in corn oil i.p.	As an *in vivo* pre-study to the subsequent *in vitro* study, one male S-D rat (275-300g) was exposed i.p. to 8:2 FTOH and one was exposed to the vehicle (corn oil) by intraperitoneal injection. Blood, liver and kidney samples were taken 6 h after exposure. Samples were analysed by HPLC/MS/MS for the parent compound and the various metabolites. Rat tissue (blood, liver and kidney) showed metabolites of 8:2 FTOH like PFOA and 8:2 FTCA and 8:2 FTUCA. A novel metabolite, PFNA was also confirmed both from *in vivo* and *in vitro* samples though at 10 fold lowere levels than the previous acids. In addition this study indicates the presence of metabolites corresponding to O-glucuronide and O-sulfate in addition to GSH conjugates and dehydrofluorination to yield α,β-unsaturated GSH conjugates. These species may play a role in the excretion or enterohepatic recirculation of FTOHs *in vivo*.	Martin, Mabury, and O'Brien, 2005
CD-1 mice	30 mg/kg bw 8:2 FTOH solved in deionized water: polypropylene glycol (1:1) Gavage	Male CD-1 mice were exposed to 8:2 FTOH by oral gavage. The animals were sacrificed 6 h after treatment and blood and liver samples were collected. Several PFCAs were detected and quantified by LC/MSMS analysis and the volatile precursor compounds were detected by GC/MS analysis. Six hours after treatment 97 ± 26 ng/ml 8:2 FTOH was detected in serum and 134 ± 42 ng/g in liver. In serum the concentration of PFOA was 972 ± 44 ng/ml and in liver 277 ± 29 ng/g while the PFNA concentration were 65 ± 15 ng/ml in serum and 60 ± 22 ng/g in liver.	Henderson et al., 2007
CD-1 mice	30 mg/kg bw 8:2 FTOH in propylene glycol/water (1:1) vehicle	Timed-pregnant CD-1 mice received a single dose of 8:2 FTOH by gavage on gestation day 8 (GD8). Maternal and neonatal serum and liver as well as foetal and neonatal homogenate extracts were analysed by GC/MS. During gestation (GD9 to GD18), maternal serum and liver concentration of PFOA decreased from 789 ± 41 to 668 ± 23 ng/ml and from 673 ± 23 to 587 ± 55 ng/g, respectively. PFOA was transferred to the developing foetuses as early as 24 h post-treatment with increasing concentration from 45 ± 9 ng/g (GD10) to 140 ± 32 ng/g (GD18), while PFNA was quantifiable only at GD18 (31 ± 4 ng/g). Post-partum, maternal serum PFOA concentration decreased from 451 ± 21 ng/ml postnatal-day (PND) 1 to 52 ± 19 ng/ml PND15 and PFNA concentrations although fivefold less, exhibited a similar trend. After birth pups were cross-fostered. with dams exposed during gestation or during lactation with 8:2 FTOH or exposed to vehicle . Pups treated during gestation and fostered by dams treated during lactation and pups exposed during gestation showed an average PFOA concentration of 200 ± 26 ng/g at PND1, decreased to 149 ± 19 ng/g	Henderson and Smith, 2006

		at PND3 and this decrease was seen in both neonatal liver and serum from PND3 to PND15. The group of pups only exposed via lactation had a PFOA concentration of 57 ± 11 ng/ml at PND3 and 58 ± 3 ng/ml at PND15. This leads to the conclusion that neonates were exposed through lactation. The exposure of both PFOA and PFNA occurred both pre- and post-natally following maternal exposure to 8:2 FTOH on GD8.	
ddY mice	0, 0.025, 0.05, 0.1 and 0.2% (W/W) 8:2 FTOH Gavage	Male ddY mice were exposed in the diet to 8:2 FTOH for 7, 14, 21 and 28 days. These treatments induced liver enlargement in a dose - and duration - dependent manner. Peroxisome proliferation in the liver was confirmed by electron microscopic examination. They showed that peroxisomeal acyl-CoA oxidase was induced by these treatments in a dose – and time – dependent manner. The concentration of PFOA and related compounds were determined in the liver and plasma. Five metabolites, PFOA, PFNA, 8:2 teleomer acid and two unidentified metabolites were present in the liver and serum. There is a strong indication that the increased peroxisome proliferation is not induced by 8:2 FTOH itself but by the metabolite PFOA since there were detected an accumulation of PFOA in the liver.	Kudo et al., 2005

Dermal:

Species	**Dose (mg/kg)**	**Observations and Remarks**	**Ref.**
Sprague-Dawley rats (Crl:CD (SD)IGS BR rats)	125 mg/kg (10 µl/cm^2). 8:2 FTOH in Methylcellulose (0.5% wt/vol)	Single dermal dose of radioactive (3-^{14}C) 8:2 FTOH in 3 females and 3 males. The substance was dosed on a clipped, shaved and washed hair free area on the shoulder (5.3 cm^2). The substance was glued to the area by Scotch Brand Crazy Glue gel and covered with gauze and wrapped with Coban. Immediately after exposure the area was covered by airtight, organic volatile trap containing untreated activated charcoal. After 6h exposure the test substance were removed and washed. The majority of the dermal dose either volatilized from the skin (37%) or was removed by washing (29%). Following the 6h dermal exposure and a 7-day collection period, excretion of total radioactivity via urine (< 0.1%) and faeces (< 0.2%) was minor, and radioactivity concentrations in most tissues were below detection limit. Based on average amount of 8:2 FTOH applied (~31,250 µg), total radioactive residues at termination were detected at site of application (21-58 µg equiv/g), in fat (0.25-0.36 µg equiv/g) and in liver (0.09-0.24 µg equiv/g). The total absorbed dose following a single 6 h exposure and a 7- day recovery collection period was low, ranging from 0.5 to 1% and was primarily due to the radioactivity at the application site. The conclusion from the study was that systemic availability of 8:2 FTOH following dermal exposure was negligible.	Fasano et al., 2006

In vitro metabolism:

Species	Dose (mg/kg)	Observations and Remarks	Ref.
Sprague-dawley rats (Crl:CD (SD)IGS BR rats)	5, 20 or 100 µM 8:2 FTOH	Rat, mouse and human hepatocytes were dosed with radioactive (3-^{14}C) 8:2 FTOH in Acetonitrile. Microsome, cytosol and hepatocytes were analysed for the amount of metabolites by LC/MS/MS. The elimination half-life in hepatocytes as indicated by the relative amount of PFOA were mouse>rats>humans>trout. The amount of PFOA produced in the microsomal incubation indicated mouse>rats. Neither PFOA nor PFNA was detected in the human microsomal reactions. Consistent with previous findings by Fasano et al., (2006) and Martin et al., (2005) this study confirms that 8:2 FTOH was metabolized to glucuronide and sulfate conjugates and also oxidized to 8:2 FTAL which by HF elimination yielded unsaturated 8:2 fluorotelomer aldehyde (8:2 FTUAL).	Fasano et al., 2006
Sprague-Dawley rats (Crl:CD (SD)IGS BR rats), CD mice (Crl:CD1 (ICR) and human hepatocytes	0, 5, 20 and 100 µM 8:2 FTOH	In vitro metabolism of [14C] 8:2 FTOH and selected acid metabolites were measured in rat, mouse and human hepatocytes, and in rat, mouse and human liver microsomes and cytosol. Hepatocytes from rats and mice at age 8-12 weeks were used. Rodent hepatocytes eliminated 8-2 FTOH ($T_{1/2}$ = 9.9–12.9 min) about 3 times faster than human hepatocytes. The clearance rate of 8:2 FTOH in hepatocytes were highest in rats then followed mice > humans. A number of metabolites were identified. Rat and mouse hepatocytes produced 5-fold and 11.9-fold more PFOA than human hepatocytes, respectively. Neither PFOA nor PFNA were detected from incubation with human microsomes. The percent of 8-2 FTOH metabolized to PFOA, based on the molar concentration detected at the end of the incubation periods, was small, 0.47, 0.24, and 0.02% for mouse, rat and human hepatocytes, respectively. The overall results indicated that 8:2 FTOH is extensively metabolized in rats and mice and to a lesser extent in humans. Metabolism of 8-2 FTOH to perfluorinated acids was small and likely mediated by enzymes in the microsomal fraction.	Nabb et al., 2007
Sprague-Dawley rats (S-D rats)	20-200 µM 8:2 FTOH	Hepatocytes were isolated from young (275-300g) male S-D rat liver perfused with collagenase. The isolated hepatocytes were exposed to 8:2 FTOH and the samples were analysed by HPLC/MS/MS for the parent compound and the various metabolites for 1-4 h. Rat hepatocytes showed metabolites of 8:2 FTOH like PFOA and PFNA and others after 1-3 h of exposure. After 4 h with 18 µM 8:2 FTOH, 78% of the parent compound had been biotransformed; 2.9 % 8:2 FTCA, 4.1 % 8:2 FTUCA, 1.4 % PFOA, and <0.2 % PFNA. Two other perfluorinates acids were detected in isolated rat hepatocytes: tetrahydroperfluoroalkyl carboxylate (THPFCA) and dihyroperfluoroalkyl carboxylate (DHPFCA). In addition aldehyde metabolites were detected. These substances are unstable except under special treatment conditions were they form stable hydrazone derivatives. Using 2,4-dinitrophenylhydrazine (DNPH) trapping, the immediate oxidation product of 8:2 FTOH was identified as 8:2 fluorotelomer aldehyde (8:2 FTAL;CF3(CF2)7CH2C(H)O). 8:2 FTAL was transient and eliminated HF non-enzymatically to yield 8:2 fluorotelomer, -unsaturated aldehyde (8:2 FTUAL; CF3(CF2)6CF CHC(H)O) which was also short-lived and reacted with GSH and perhaps other endogenous nucleophiles. Four polyfluorinated acid intermediates were also detected, including 8:2	Martin, Mabury, and O'Brien, 2005

		fluorotelomer carboxylate (8:2 FTCA; CF3(CF2)7CH2C(O)O−), 8:2 fluorotelomer ,-unsaturated carboxylate (8:2 FTUCA; CF3(CF2)6CFCHC(O)O−), tetrahydroperfluorodecanoate (CF3(CF2)6(CH2)2CO2−), and dihydroperfluorodecenoate (CF3(CF2)6CH CHCO2−). The pathways leading to 8:2 FTCA and FTUCA involve oxidation of 8:2 FTAL, however, the pathways leading to the latter two polyfluorinated acids remain inconclusive. Although significant, the low molar balance for the quantifiable acid metabolites, including PFOA, indicates that they are not the major metabolic fate of FTOH in rat hepatocytes.	

5.1.1 Summary and discussion of toxicokinetics

Several studies show that FTOH compounds are metabolized to their carboxylic moiety, such as PFOA. A number of metabolites have been detected in the urine, serum, liver and kidney of mice. 8-2 FTOH are preferentially distributed to the fat tissue, while the metabolites are generally found at greater concentrations in lean, highly perfused tissues, and in mice most metabolites are more highly concentrated in the liver.

The metabolism of 8-2 FTOH is rapid and most of the parent compound is biotransformed at 6 h post-treatment *in vivo* and between 1-3 h *in vitro*. Martin and co-workers determined that at 4 h post-treatment *in vitro*, 78% of the parent FTOH had been metabolized; however, metabolites only accounted for approximately 8.5% total molar mass (Martin, Mabury and O'Brien, 2005).

In the study of Fasano and co-workers (Fasano et al., 2009) of rats orally exposed daily to 8-2 FTOH for 45 days, and analysed at day 53, the net systemic uptake of 8-2 FTOH was 3-1.5 fold higher in females than in males. The major metabolites in urine were PFOA, 7-2 sFTOH-gluc (females only) and 8-2 uFTOH-SCysNAcetyl (females only). In plasma females had higher levels of 8-2 FTOH than males whereas males had higher levels of the downstream metabolite PFOA than females. Females on the other hand, had higher levels of upstream metabolites such as 8-2 FTA and 7-3 acid than males in plasma. These dissimilarities suggest differences in ADME between the sexes. In the liver and kidney males had significantly higher levels of PFOA compared to females, whereas the levels of 8-2 FTA were higher in females than males and the levels of 7-3 acid were similar between the sexes. 8-2 FTOH and most metabolites were rapidly or completely cleared from the tissues, with the exception of 7-3 acid and PFOA (particularly in males), which exhibited much slower rates of clearance. In males the concentration of PFOA increased during the 45 days of exposure, which suggest slow elimination.

In a 90-day oral gavage study in rats Ladics and co-workers (Ladics et al., 2008) reported that PFOA accounts for the majority of the fluorinated substances in males (85%) at 125 mg/kg /day, and that PFOA accounted for a large portion of the fluorine present in plasma in males, which was not the case for females. In males, the highest concentration of PFOA was found in the liver at the lower doses and in plasma at the highest dose.

Nabb et al. studied the *in vitro* metabolism of [^{14}C] 8:2 FTOH and selected acid metabolites in rat, mouse, trout and human hepatocytes in addition to rat, mouse and human liver microsomes and cytosol. The clearance rate of 8:2 FTOH in hepatocytes were highest in rats then followed mice > humans. Neither PFOA nor PFNA were detected from incubation with human microsomes.

Henderson and Smith (Henderson and Smith, 2007) showed that when pregnant rats were administrated 8:2 FTOH the metabolites PFOA and PFNA were detected in the neonates.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Species	LD50 (mg/kg)	Observations and Remarks	Ref.
		Acute toxicity:	
Sprague-Dawley rats (Crl:CD®(SD)IGS BR rats)	> 2000 mg/kg	Range finding study Single intragastric intubation to male and female rats according to OECD Test Guideline 420. Female rats were administered 500 mg/kg and males 2000 mg/kg. No toxicity was reported. Main study Five male and female rats were given single intragastric intubation of 2000 mg/kg according to OECD Test Guideline 420. No mortality or clinical signs of toxicity were reported. There were no body weight loss and no gross lesions were present at necropsy. Minimum lethal dose = 2000 mg/kg	Finlay C, 2008

5.2.2 Acute toxicity: inhalation

No data available

5.2.3 Acute toxicity: dermal

No data available

5.2.4 Acute toxicity: other routes

No data available

5.2.5 Summary and discussion of acute toxicity

Only an oral acute toxicity study with 8:2 FTOH was available. The LD50 value from the acute toxicity study was ≥ 2000 mg/kg (limit dose). No classification for oral acute toxicity is proposed.

5.3 Irritation

5.3.1 Skin

No data available

5.3.2 Eye

No data available

5.3.3 Respiratory tract

No data available

5.3.4 Summary and discussion of irritation

No data were available on the irritating properties of 8:2 FTOH following skin, eye and respiratory exposure. No conclusion can draw on classification of 8:2 FTOH for irritation.

5.4 Corrosivity

No data available

5.5 Sensitisation

5.5.1 Skin

No data available

5.5.2 Respiratory system

5.5.3 Summary and discussion of sensitisation

No data were available on skin and respiratory sensitization following exposure to 8:2 FTOH. No conclusion can draw on classification of 8:2 FTOH for sensitization.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Species	Dose mg/kg body weight, mg/kg diet	Duration of treatment	Observations and Remarks	Ref.
Sprague-Dawley rats (Crl:CD®(SD)IGS BR rats)	0, 5, 25, 125 mg/kg bw/day 8:2 FTOH	84 days of exposure, 75 days recovery	Extended range finding study. The toxicokinetic information is given in 5.1. Young adult rats were administered 8:2 Telomer B alcohol by oral gavage. 10 males/group and 5 females/group. The animals were exposed to the various doses of 8:2FTOH until steady state of fluorine in blood, around 60-84 days post-dosing. At steady state blood fluorine levels, the liver and kidneys of 5 males/group were weighted. At the end of the study liver kidney and fat were analysed for 8:2 FTOH, PFOA and PFNA from both males and females. In addition, pooled plasma samples obtained from males and females over the duration of the in-life phase of the study were analysed for 8:2 FTOH, 8:2 acid, PFOA and PFNA. At steady state (day 84) pooled plasma were analysed for 8:2 FTOH, PFOA and total fluorine levels. A recovery period of 75 days was included. No test related mortality was reported. A test substance-related statistically significant increase was observed in the striated teeth at 125 mg/kg/day in both males and females. There was a decrease in body weight and body weight gains in male rats at 125 mg/kg/day at day 81. Body weight was similar to control at the end of the recovery period. In females there were no changes in either body weight or bodyweight gains. There were a test substance related and statistically significant increase in relative liver weight in males administered 125 mg/kg/day at day 81 (females not sacrificed at this time point). After 75 days of recovery in males, liver weights were reversed to normal whereas relative kidney weights seemed to be increased in a dose-dependent manner (non significant increases). After 75 days of recovery a test substance related and statistically significant increases in liver and kidney weights were observed in females administered 125 mg/kg/day. No histopathological examination was performed.	Ladics, 2001
Sprague-	0, 1, 5, 25,	90 days, 3	8:2 Telomer B alcohol: subchronic toxicity. 90-day	Ladics et

Dawley rats (Crl:CD®(SD)IGS BR rats)	125 mg/kg bw/day 8:2 FTOH in 0,5 % aqueous methylcellulose	month recovery group	oral gavage study in rats (15 rats/sex/dose). A 3 month recovery group were included for animals in control and high-dose groups only. In addition, 5 rats/sex/dose were designated for hepatic biochemical analysis following a 10-day exposure. Clinical parameters were evaluated at week 7 and 13. No test substance related mortality. A test substance-related statistically significant increase was observed in the striated teeth at 125 mg/kg/day in both males and females. No test substance related changes in body weight or body weight gain, food intake or food efficiency in any of the dose groups neither for females nor males were reported. There were no reported exposure-related effects on the neurobehavioral tests performed. The rate of hepatic β-oxidation was measured after 10 and 90 days of exposure and in the 3-month recovery groups. In males an increase in β-oxidation was observed in the high-dose group (ap. 160% during exposure and 130% after recovery). In females an increase in β-oxidation was observed in the high-dose group (130% and 152% following 10 days and 90 days exposure, respectively), but returned to control level in the recovery group. A statistically significant increase in hepatic ß-oxidation was also observed in females exposed to 25 mg/kg/day at the 90-day time-point. The test substance was considered a mild inducer of hepatic peroxisomal β-oxidation in rats. A test-substance related statistically significant increase in liver weight was reported in females from 25 mg/kg bw/day and in males and females from 125 mg/kg bw/day. Liver weights returned to normal in the recovery groups. Increased liver weight was associated with microscopic hepatocellular hypertrophy at 125 mg/kg bw/day in males only. This effect was considered to be a physiological adaptive response to the metabolism of 8:2 FTOH and not adverse. Following 90 days exposure, a test-substance-related adverse increase in the incidence and severity of focal hepatic necrosis was reported in males at 25 mg/kg bw/day (5/10 animals) and at 125 mg/kg bw/day (3/10 animals). No necrosis was observed in control animals. The necrosis was accompanied by a minimal inflammatory response. After 3 months of recovery the incidence of hepatocelluar necrosis in male rats was increased at 125 mg/kg bw/day (7/10 animals) compared to controls (3/10 animals).	al., 2008

			A test-substance related statistically significant increase in kidney weight was reported in males and females from 25 mg/kg bw/day during exposure, but not in the recovery groups. Moreover, microscopic renal tubular hypertrophy was observed from 25 mg/kg bw/day in males only. However, no correlative microscopic or clinical pathological evidence of renal toxicity were present. Therefore, the kidney weight changes and microscopic hypertrophy were not considered adverse findings. A test-substance-related adverse increase in the incidence and severity of chronic progressive nephropathy was reported in females at 125 mg/kg bw/day. After 3 moth of recovery the incidence and severity of chronic progressive nephropathy increased at 125 mg/kg bw/day in females. The incidence and/or degree of thyroid gland lesions (altered colloid) were increased in males of all dose groups. Altered thyroid colloids occurs spontaneously in Sprague-Dawley rats and increases with age. The test substance related increase in thyroid lesions was not considered adverse as there were no other microscopic alterations observed. Other treatment related effects at 25 mg/kg/d was reduced red cell mass, reticulocytosis, increased serum cholesterol, increased alkaline phosphatase, decreased trigycerid, increased protein, albumin and calcium levels, increased urine volume and decreased urine ketone concentration. The plasma fluorine levels increased in the dosing period in the highest dose-groups (largest increase in females), but three months post treatment the plasma fluorine levels were similar to controls. Urine fluorine were increased in a dose-dependent manner. After 3 months recovery, total urine fluorine were approximately 3 times greater than controls in males and slightly greater in the females of the high-dose groups, indicating continued metabolism of the test substance. The enamel organ ameloblast cells were degenerated and disorganised in rats of the high-dose group. These lesions were still present in some animals of the recovery group and were considered an adverse effect caused by fluoride toxicosis. Under the conditions of the study, the NOAEL for 8:2 FTOH for males was 5 mg/kg bw/day based on the incidence of hepatic necrosis from 25 mg/kg bw/day. The NOAEL for females was 25 mg/kg bw/day based on the incidence and severity of chronic progressive nephropathy at 125 mg/kg bw/day.	

Sprague-Dawley rats	0, 25, 100, 250 mg/kg bw/day of a test substance of fluoroalkyletanol (FTOH mixture CAS no. 65530-60-1, 95 % purity, containing 27% 8:2 FTOH)	90 days	All animals were treated daily by gavage and the test substance was solved in aqueous methylcellulose. No test substance – related mortality or neurotoxicity was reported. Body weights and /or nutritional parameters were significantly reduced at 100 and 250 mg/kg bw/day, and these effects were reversible. Broken and absent teeth were observed in rats dosed with 250 mg/kg bw/day, and microscopic tooth lesions occurred at 100 and 250 mg/kg bw/day and persisted with decreased severity throughout recovery. Decreased red cell mass parameters occurred at 90 days in the 250 mg/kg bw/day group, but red cell counts were normal thereafter during recovery. Statistically significant increases in liver weight parameters were present in males and females administered 25 (males only), 100, or 250 mg/kg bw/day for 90 days. The increased liver weights correlated with microscopic hepatocellular hypertrophy in the two highest dose groups. Hepatic β-oxidation was increased in a dose-dependent manner and persisted through 1 month of recovery at 250 mg/kg bw/day. Increased kidney weights were observed at 25 (females only), 100 and 250 mg/kg bw/day. These elevated weights persisted in the high dose group after recovery and correlated with microscopic tubular hypertrophy (males only). Thyroid follicular hypertrophy was present at 100 and 250 mg/kg bw/day but was not present after recovery. Total fluorine in whole blood increased continuously with dosing and achieved steady state in approximately 42 days. Both plasma and urine fluoride levels were elevated in a dose-dependent manner.	Ladics et al., 2005
Sprague-Dawley rats (S-D rats).	Oral by gavage 0, 25, 100 and 250 mg/kg/day as a suspension in 0,5 % aqueous methylcellulose of a mixture of FTOHs (27% 8:2 FTOH)..	Daily exposure. Animals were exposed 74 days prior to cohabitation and during mating, gestation and lactation.	The P1 generation was evaluated for several parameters like body weights, feed consumption, clinical signs, gross pathology, sperm parameters, oestrous cycle and reproductive performance. A statistically significant decrease in bodyweight at the 250 mg/kg /d group during and after the cohabitation period, but no concomitant reduction in bodyweight gain in P1 males during that period. No test-substance related clinical signs of toxicity were observed in the P1 or F1 generation rats. There was an increase in tooth clipping required in males administered 250 mg/kg/d, consistent with dental problems in the sub-chronic toxicity study of Ladics et al.(2005). There were no test-substance related effects on oestrous cycle parameters, sperm morphology and motility or epididymal sperm counts in the P1 generation. At 100 and 250 mg/kg/d there was a statistical significant increase in testicular spermatid numbers in the P1 male rats. This was not considered test-substance related because the means for these groups were within the	Mylchreest et al., 2005 a

			historical control range for previous studies. The increase appeared to be due to slightly lower than usual mean weight in the control groups. There were no toxicologically significant pathology findings in the P1, F1 pups or F1 generation adult rats. The NOAEL in the P1 generation for systemic toxicity was 100 mg/kg/day based on a statistically significant reduction in body weights, and increase in tooth clipping required in males at 250 mg/kg bw/day.	

5.2.6 Repeated dose toxicity: inhalation

No data available.

5.2.7 Repeated dose toxicity: dermal

No data available.

5.2.8 Other relevant information

Repeat-dose studies in rats and mice demonstrated that the liver is the primary target organ of the 8:2 FTOH metabolite PFOA. Due to gender differences in elimination, adult male rats exhibit effects at lower administered doses than adult female rats. The classification for PFOA was agreed in the former TC C&L group in October 2006 for repeated dose toxicity with Xn;R48/22 and T;R48/23 (classification according to CLP: STOT RE 2, H373 and STOT RE 1, H372) for oral and inhalation exposure, respectively.

5.2.9 Summary and discussion of repeated dose toxicity:

Oral: In a 90 day oral repeated dose toxicity study (Ladics et al. 2008; key study) a test-substance related adverse increase in the incidence and severity of focal hepatic necrosis was reported in males from 25 mg/kg bw/day. After a recovery period of 3 months the incidence of hepatocellular necrosis increased in the 125 mg/kg bw/day dose group in males. In females a test-substance-related adverse increase in the incidence and severity of chronic progressive nephropathy was reported at 125 mg/kg bw/day. After a 3 month recovery period the incidence and severity of chronic progressive nephropathy was increased at 125 mg/kg bw/day in females. Based on the liver toxicity in males at ≥ 25 mg/kg bw/day a classification according to CLP classification criteria with STOT RE.2, H373 (Xn; R48/20/22) for 8:2 FTOH is proposed. The CLP guidance values (oral, rat) for Cat. 2 (90 d) is a significant toxic effect observed within 10 < C <= 100 mg/kg bw/d. Similarly classification as Xn; R48 for effects occurring within 5<C<=50 mg/kg bw/d according to Directive 67/548/EEC.

This proposal is supported by studies reporting hepatotoxic effects of PFOA, the major metabolite of 8:2 FTOH in male rats. The peak plasma PFOA level (36 µg/ml) measured in male rats at the 125 mg 8-2 FTOH/kg bw/day dose level in a 45 days toxicokinetic study (Fasano et al.2009), was reported to be within the range of plasma PFOA concentrations associated with minimal to mild

hepatic hypertrophy (20–51µg/ml) where PFOA alone was administered to rats at 1mg/kg bw/day. This observation was also said to be consistent with results for a 13-week PFOA feeding study in rats where minimal to mild hypertrophy was also observed, but at a slightly lower dose of 0.64 mg/kg bw/day with a corresponding serum PFOA level of 41µg/ml (Fasano et al., 2009). PFOA is not metabolized further and it is likely to contribute to the hepatotoxicity of 8:2 FTOH.

5.3 Mutagenicity

5.3.1 In vitro data

Test	Species	Conc. (µg/plate)	Metabolic activ.	Observations and Remarks	Ref.
OECD - 409	S. typhimurium TA 98, TA 100, TA 1535, TA 1537 and E.coli WP2uvrA	0, 33.3, 100, 333, 1000, 3330 and 5000	± S9	Purified 8:2 Alcohol (Haskell Number 24691) was tested in triplicate in a Salmonella e-coli reverse mutation assay with DMSO as vehicle. No toxicity was observed at any dose levels with and without S9. The study did not fulfil the criteria for positive response concerning mean number of revertants/plate. The positive control for TA 1537 without S9 was not fulfilled. The other positive controls were according to the recommendation. Conclusion: negative for mutation in vitro.	Covance study 22900-0-409OECD

5.3.2 In vivo data

Test	Species	Conc. (mg/kg)	Metabolic activ.	Observations and Remarks	Ref.
OECD – 454 Range-finding study	Male Crl:CD®(SD) IGS BR rats	2000		Limit dose *in vivo* rat micronucleus assay by oral gavage in 3 males and 3 females with 0.5 % methylcellulose as vehicle. Conclusion: No lethality or clinical toxicity was reported.	Covance Study: 22900-0-454OECD
OECD – 454	Male Crl:CD®(SD) IGS BR rats	0, 500, 1000 and 2000		In vivo rat micronucleus assay by oral gavage in 6 males/dose/harvest time points with 0.5 % methylcellulose as vehicle. Cyclophosphamide (60 mg/kg bw) was used as a positive control and	Covance Study: 22900-0-454OECD

				analysed at 24 h post treatment. Bone marrow was harvested from 5/6 rats at 24 h and 48 h after treatment. There were no lethality or sign of clinical toxicity post dosing and no detection of cytotoxicity up to 2000 mg/kg bw. No statistically significant increase in MNPCE at any dose levels. Conclusion: The effect of 8:2 FTOH is considered negative in rat micronucleus assay under the current test conditions up to limit dose.	

5.3.3 Human data

No data available

5.3.4 Other relevant information

No data available

5.3.5 Summary and discussion of mutagenicity

Based on the two reports available on genotoxicity of 8:2 FTOH there seems to be no concern for genotoxicity. This is also supported with the findings from two other genotoxicity studies on a mix of several FTOH's (27% 8:2 FTOH) which both were negative (Gudi R and Brown C DuPont-5580 (Gudi R and Brown C) and Wagner WO and Klug ML DuPont-5579(Wagner VO and Klug ML)). No classification for mutagenicity is proposed.

5.4 Carcinogenicity

5.4.1 Carcinogenicity: oral

No data available

5.4.2 Carcinogenicity: inhalation

No data available

5.4.3 Carcinogenicity: dermal

No data available

5.4.4 Carcinogenicity: human data

No data available

5.4.5 Other relevant information

8:2 FTOH is metabolised to PFOA.

5.4.6 Summary and discussion of carcinogenicity

The *in vitro* and *in vivo* mutagenicity studies were negative. No carcinogenicity studies were available for 8:2 FTOH. Thus, the data are insufficient to evaluate the carcinogenicity of 8:2 FTOH and no classification is proposed.

5.5 Toxicity for reproduction

5.5.1 Effects on fertility

Species	Route	Dose	Exposure time (h/day)	Number of generations exposed	Observations and Remarks	Ref.
Sprague-Dawley rats 20/sex/group	Oral gavage	0, 25, 100, 250 mg/kg bw/day of the mixture of FTOHs (27% 8:2 FTOH).	Daily for a period of 74 days before cohabitation during mating, gestation and lactation.	One generation	Three weeks prior to cohabitation with males vaginal smears were collected daily from all P1 females to evaluate the oestrous cycle until copulation was confirmed. Sperm parameters for the first 10 of the 20 P1 males in each exposure group were evaluated. The right cauda epididymis was weighted and sperm were evaluated for motility and morphology. The left cauda epididymis and testis were frozen for later quantification. At postnatal day (PND) 0, 4, 7, 14 and 21 live pups were counted by sex and weighed. They were also examined for abnormal behaviour and appearance, any dead missing or abnormal pups were recorded. F1 generation male and female rats were monitored daily for vaginal opening (beginning PND 21) or perputial separation (beginning PND	Mylchreest et al., 2005 a

					35) until criterion was achieved, and body weight was recorded at the day of achievement. **Results:** *Systemic toxicity*; No test-substance related mortality occurred in the P1 and F1 generation rats. However, one female rat died in each of the 100 and 250 mg/kg/d groups. This seems not to be related to the test substance. A significant decrease in bodyweight in the 250 mg/kg /d group during and after cohabitation period (10 % reduction), but no concomitant reduction in bodyweight gain in P1 males during that period. No test-substance related clinical signs of toxicity were observed in the P1 or F1 generation rats. There was an increase in tooth clipping required in males administered 250 mg/kg/d, consistent with dental problems in the sub-chronic toxicity study of Ladics et al.(2005). The NOAEL for systemic toxicity was 100 mg/kg bw/day based on body weight reduction. *Reproductive toxicity:* There were no test-substance related effects on oestrous cycle parameters, sperm morphology, motility or epididymal sperm counts in the P1 generation. At 100 and 250 mg/kg/d there was a statistical significant increase in testicular spermatid numbers in the P1 male rats. This was not considered test-substance related because the means for these groups were within the historical control range for previous studies. The increase appeared to be due to slightly lower than usual mean weight in the control groups. Litter size at birth was reduced from 100 mg/kg bw/day (14.7, 13.4, 12.4 and 12.5 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively), and number of live pups per litter on day 0 (14.6, 13.2, 11.3 and 12.1 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively) and on lactation day 4 (14.6, 12.9,	

					10.8, 11.8 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively). At 250 mg/kg bw/day a statistically significant reduction in pup weights on pnd 4, 7, 14, and 21 was reported, that was 74-78 % of control values on pnd 21 in males and females. There were no toxicologically significant pathology findings in the F1 pups or P1 or F1 generation adult rats. NOAEL for the FTOH mixture containing 27 % 8:2 FTOH reproductive toxicity was 25 mg/kg/d based on litter size reduction.	

5.5.2 Developmental toxicity

Species	**Route**	***Dose mg/kg/day ppm **Conc. (mg/l)**	**Exposure time (h/day)**	**Exposure period: - number of gene-rations or - number of days during pregnancy**	**Observations and Remarks**	**Ref.**
Sprague-Dawley rats (Crl:CD® (SD)IGS BR rats), 22/group	Oral by gavage	0, 50 ,200 or 500 mg/kg/day of 8:2 FTOH B alcohol.	daily	Gestation days 6-20.	In the developmental toxicity study groups of time-mated female rats were given 0, 50, 200 or 500 mg/kg/day 8:2 FTOH by oral gavage from gestation day 6-20. At day 21 all surviving dams were sacrificed. The abdominal and thoracic viscera were examined and the uterus from each rat were removed and dissected for examination of the uterine content. The doses were chosen based on a repeated dose range finding study (DuPont-6357). *Maternal toxicity:* Four dams in the highest dose group were sacrificed in extremis on gestation day (gd) 10, 11, 12 or 18, and one dam was found dead on gd 16. Clinical observations in the highest	Mylchreest, Munley, and Kennedy, Jr., 2005 b.

					dose group included increased occurrence of alopecia, diarrhoea, hunched-over posture, weakness and fur-staining. There were no clinical observations at 50 or 200 mg/kg bw/day. At 500 mg/kg bw/day the mean maternal weight gain over the course of the study (gd 6-21) was 25% lower compared to the control group, and the mean final maternal body weight was statistically significant reduced (around 10 %) compared to control group. A statistically significant reduction in food consumption was reported at 500 mg/kg bw/day, and occasionally at 200 mg/kg bw/day, however, the reduction was not considered as adverse toxicity. In the highest dose group necropsy observations included pale kidneys in one dam, however, the other dams appeared normal. The NOAEL for maternal toxicity was 200 mg/kg bw/day. *Developmental toxicity*: No effects were reported on the number of corpora lutea, implantation sites, litter size, resorptions, foetal weight, and sex ratio. No malformations were reported. An exposure-related statistically significant increase in skeletal variations was reported from 200 mg/kg bw/day. These included at 500 mg/kg bw/day an increase in the occurrence of delayed pelvic bone ossification and wavy ribs and from 200 mg/kg bw/day an increase in the incidence of delayed skull bone ossification. However, the range of skull bone ossification was within the range of the historical control data, and was observed in the absence of a test-substance	

					related effect on foetal body weight. The NOAEL for developmental toxicity in rats was 50 mg/kg bw /day.	
Sprague-Dawley rats (S-D rats). 20/sex/ group	Oral by gavage	0, 25, 100 or 250 mg/kg/day of FTOH mixture (27% 8:2 FTOH).	daily	One generation. For a period of 74 days prior to cohabitation, during mating, gestation and lactation.	In the one-generation toxicity study groups of time-mated female S-D rats were given 0, 25, 100 or 250 mg/kg/day of a commercial mixture of different FTOH (27% 8:2 FTOH). Body weight, feed consumption, clinical signs, gross pathology, sperm parameters, oestrous cycle and reproductive performance were evaluated for the P1 generation. The F1 offspring were evaluated during the lactation period for growth and survival and given a gross pathology examination at weaning. A subset of the offspring were retained and evaluated for changes in body weights, feed consumption, clinical signs, and age at onset of vaginal opening and pre-pubertal separation. Gross pathology was performed on postnatal day 60. **Results:** *Systemic toxicity*; No test-substance related mortality occurred in the P1 and F1 generation rats. However, one female rat died in each of the 100 and 250 mg/kg/d groups. This seems not to be related to the test substance. A significant decrease in bodyweight at the 250 mg/kg /d group during and after cohabitation period (10 % reduction), but no concomitant reduction in bodyweight gain in P1 males during that period. No test-substance related clinical signs of toxicity were observed in the P1 or F1 generation rats. There was an increase in tooth	Mylchreest et al., 2005 a.

					clipping required in males administered 250 mg/kg/d, consistent with dental problems in the subchronic toxicity study of Ladics et al.(2003). The NOAEL for systemic toxicity was 100 mg/kg bw/day. *Reproductive toxicity:* Litter size at birth was reduced from 100 mg/kg bw/day (14.7, 13.4, 12.4 and 12.5 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively), and number of live pups per litter on day 0 (14.6, 13.2, 11.3 and 12.1 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively) and on lactation day 4 (14.6, 12.9, 10.8, 11.8 in the 0, 25, 100 and 250 mg/kg bw/day dose group, respectively). At 250 mg/kg bw/day a statistically significant reduction in pup weights on pnd 4, 7, 14, and 21 was reported, that was 74-78 % of control values on pnd 21 in males and females. There were no toxicologically significant pathology findings in the F1 pups or F1 generation adult rats. The NOAEL for developmental toxicity for the FTOH mixture containing 27 % 8:2 FTOH was 25 mg/kg/day.	
Sprague-Dawley rats (S-D rats). 20/rats/ group	Oral by gavage	0, 50, 200 or 500 mg/kg/day of FTOH mixture (27% 8:2 FTOH).	daily	Gestation days 6-20.	In the developmental toxicity study groups of time-mated female S-D rats were given a commercial mixtures of FTOH (27% 8:2 FTOH). On day 21 of gestation dams were sacrificed and the thoracic and abdominal viscera were examined. The uterine contents were removed and examined, and foetuses were evaluated for alterations. In this study there was detected 5% reduction in maternal body	Mylchreest et al., 2005 b.

					weight, increased perinatal fur staining, and increased foetal skeletal alterations at 500 mg/kg/day. There were no maternal or developmental toxicity at the lower doses. Based on these findings the NOAEL for developmental toxicity of the mixture of FTOHs containing 27 % 8:2 FTOH was 200 mg/kg/day.	

5.5.3 Human data

5.5.4 Other relevant information

8:2 FTOH is metabolised to PFOA. Animal experiments with PFOA has shown to induce increased postnatal pup mortality, decreased pup body weight and delayed sexual maturation in the absence of marked maternal toxicity.

The classification for PFOA was agreed in the former TC C&L group in October 2006 for reproductive toxicity with Repr. Cat.2 R61 (classification according to CLP: Repr. 1B, H360D). A toxicokinetic study (Fasano et al. 2009) has shown that following 8:2 FTOH exposure of rats, the blood level of PFOA is much higher in males than in females. The low biotransformation of 8:2 FTOH to PFOA in female rats makes the relevance of the PFOA effects for the evaluation of developmental toxicity of 8:2 FTOH uncertain.

5.5.5 Summary and discussion of reproductive toxicity

Fertility

In a one-generation study in rats exposed to a mixture of FTOHs with 27 % 8:2 FTOH no effects were reported on sperm parameters, oestrus cycle and reproductive performance in rats up to 250 mg/kg bw/day. No classification for fertility is proposed.

Development

In a developmental toxicity study with exposure to 8:2 FTOH from gestation day 6-20 no malformations were reported. However, an increase in skeletal variations was reported from 200 mg/kg bw/day. These included at 500 mg/kg bw/day an increase in the occurrence of delayed pelvic bone ossification and wavy ribs and from 200 mg/kg bw/day an increase in the incidence of delayed skull bone ossification. However, the range of skull bone ossification was within the range of the historical control data, and was observed in the absence of a test-substance related effect on foetal body weigh. Severe maternal toxicity was reported at 500 mg/kg bw/day and included test-substance related mortality and a 25% reduction in mean weight gain from gestation day 6-21.

A one-generation study and a developmental toxicity study were performed with a commercial mixture of FTOH which contained 27 % 8:2 FTOH. In the one-generation study litter size at birth and the number of live pups per litter on day 0 and pnd 4 was reduced from 100 mg/kg bw/day. At 250 mg/kg bw/day a statistically significant reduction in pup weights on pnd 4, 7, 14, and 21 was reported, that was 74-78 % of control values on pnd 21. These effects were reported in the presence of a 10 % reduction in maternal body weight at 250 mg/kg bw/day. In the developmental toxicity study increased foetal skeletal alterations were reported at 500 mg/kg/day in the presence of 10% reduction in maternal body weight.

Since the increase in skeletal variations from 200 mg/kg bw/day in the developmental toxicity study with 8:2 FTOH was reported in the absence of a reduction in foetal body weights, and was within the range of the historical control data, as well as the slight effects reported in the one-generation study and developmental toxicity study with the mixture of FTOH containing 27 % 8:2 FTOH no classification for developmental effects is proposed.

5.6 Other effects

5.7 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

A harmonized classification of 8:2 Fluorotelomer alcohol (8:2 FTOH) for repeated dose toxicity with Xn; R48/20/22 according to Directive 67/548/EEC or with STOT RE 2. H373 according to the CLP/GHS criteria is proposed. Harmonized classification and labeling of substances is considered a Community wide action under Article 36 (3) in the CLP regulation (EC-regulation 1272/2008) and it is recommended that the classification proposal is considered for inclusion in Annex VI of Regulation 1272/2008/EC.

FTOHs are used as raw material in the manufacture of various products; among these the 8:2 FTOH represents the largest volume globally. 8:2 FTOH is mainly used for coating of textiles, paper and carpets to achieve oil, stain and water repellent properties and is present as residual raw materials. A Norwegian study showed that by extraction of a Norwegian "all weather coat" levels of nearly 1000 µg/m^2 8:2 FTOH and approximately 20 µg/m^2 PFOA were measured (Berger and Thomsen, 2006). In the environment, emitted 8:2 FTOH can biodegrade to the more persistent PFOA, and will thus contribute to the total environmental and human PFOA burden. The concentration of PFOA in human serum is in the ng/mLlevel (Haug et al., 2009).

The classification for PFOA was agreed in the former TC C&L group in October 2006 for repeated dose toxicity with Xn;R48/22 and T;R48/23 (classification according to CLP: STOT RE 2, H373 and STOT RE 1, H372) for oral and inhalation exposure, respectively. PFOA is a metabolite of 8:2 FTOH in mammals and is considered to contribute to the hepatotoxicity of 8:2 FTOH observed in male rats (Fasano et al., 2009). Due to the liver toxicity of 8:2 FTOH, its contribution to environmental contamination of PFOA as well as its wide spread use it is considered important to communicate the substance's properties both to the general population and industrial users by proposing a harmonised classification for repeated dose toxicity.

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

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ANNEX

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