CLH Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Perfluorooctanoic acid (PFOA)

EC Number: 206-397-9

CAS Number: 335-67-1

The classification of Perfluorooctanic acid (PFOA) was agreed in the former TC C&L group. The discussion and conclusions from the TC C&L group on the classification of PFOA is included in Annex I of this CLH dossier.

Annex I: Summary Record of PFOA and it salts from the TC C&L group meeting 21-24 March 2006 and 4-5 October 2006.

Submitted by : Climate and Pollution Agency (Norway)

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Perfluorooctanoic acid (PFOA)

EC Number: 206-397-9

CAS number: 335-67-1

Registration number (s):

Purity: 98%

Impurities: -

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

R-phrase(s):

Carc. Cat 3; R40

Repr. Cat. 2: R61

T; R48/23

Xn; R48/22, R20/22,

Xi; R36

Proposed classification based on GHS criteria:

Carc. 2, H351

Repr. 1B, H360D

STOT RE 1, H372

STOT RE 2, H373

Acute Tox. 3, H331

Acute Tox. 3, H301

Eye Irrit. 2, H319

Proposed labelling:

Class of danger: Toxic; irritant

R phrases: 40-61-48/23-48/22-20/22-36
S phrases: 53-45

Proposed labelling based on CLP Regulation:
Pictogram: GHS07, GHS08
Signal word: Danger
Hazard statement codes: H351, H360D, H372, H373, H331, H301, H319
Precautionary statements: Not required as PS are not included in Annex VI

Proposed specific concentration limits (if any): -

Proposed notes (if any):

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

PFOA is used as a group name for PFOA and its salts , and PFOA is mainly produced and used as its ammonium salt, ammoniumpentadecafluorootanoate (APFO, CAS Number: 3825-26-1). However, the perfluorooctanoate anion is the molecule of primary interest. APFO and PFOA are sometimes used interchangeably as both PFO-anion and PFOA (neutral species) exist in solution.

For systemic effects it might be assumed that both substances (APFO and PFOA) are mainly available to cells with its physiological pH in form of the corresponding anion (PFO). That might be the central justification for read across for systemic effects.

For local effects available literature indicates that PFOA and APFO in water yield acidic pH values. The differences in the pH values are considered small and therefore read across for local effects is considered relevant. In addition no studies on the human health hazard of PFOA are performed. Therefore, we suggest basing the CLH-proposal for PFOA on a read-across from APFO. See the CLH dossier for APFO for the assessment of human health hazard for PFOA.

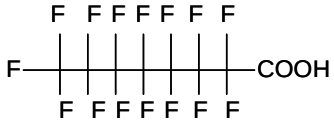
We have only included the CLH-proposal for the ammonium salt (APFO) at this stage because most of the studies are performed with APFO. Furthermore, we found it important to reach agreement on a harmonised classification of APFO/PFOA first, and then as a possible further step it could be considered to make CLH-proposals for the other salt as well. The other salts are as following: Sodium salt of PFOA CAS No: 335-95-5; Potassium salt of PFOA CAS No: 2395-00-8; Silver salt of PFOA, CAS No: 335-93-3; Fluoride acid of PFOA CAS No: 335-66-0; Methyl esther of PFOA CAS No: 376-27-2 and ethyl esther of PFOA CAS No: 3108-24-5.

1.1 Name and other identifiers of the substance

Chemical Name:	Perfluorooctanic acid (PFOA)
EC Name:	Pentadecafluorooctanoic acid (PFOA)
CAS Number:	335-67-1
IUPAC Name:	Pentadecafluorooctanoic acid

1.2 Composition of the substance

Chemical Name:	Perfluorooctanic acid (PFOA)
EC Number:	206-397-9 (PFOA)
CAS Number:	335-67-1 (PFOA)
IUPAC Name:	Pentadecafluorooctanoic acid
Molecular Formula:	C8HF15O2 (PFOA)

Structural Formula:	PFOA 
Molecular Weight:	PFOA: 414.09
Typical concentration (% w/w):	98% , impurities: not known.
Concentration range (% w/w):	

1.3 Physico-chemical properties

Table 1: Summary of physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20℃ and 101.3 KPa	3.1	PFOA is a solid.	Kirk-Othmer, 1994
VII, 7.2	Melting/freezing point	3.2	PFOA: 52 – 54 ^{o}C PFOA: 54.3 ^{o}C	Kirk-Othmer, 1994 Lide, 2003
VII, 7.3	Boiling point	3.3	PFOA: 189 ^{o}C PFOA: 189-192 ^{o}C/736 mm Hg	Kirk-Othmer, 1994. Boit, 1975
VII, 7.4	Relative density	3.4 density	PFOA: Density/specific gravity. 1.792 g/ml	Kirk-Othmer, 1994
VII, 7.5	Vapour pressure (Pa)	3.6	PFOA: 4.2 (25 ^{o}C) extrapolation from measured data PFOA: 2.3 (20 ^{o}C) extrapolation from measured data PFOA: 128 (59.3 ^{o}C) measured	Kaiser et al., 2005; Washburn et al., 2005 Washburn et al., 2005 Washburn et al., 2005
VII, 7.6	Surface tension	3.10		
VII, 7.7	Water solubility (g/L)	3.8	PFAO: 3.4 PFOA: 9.5 PFOA: 4.14	**Temperature (^{o}C)** 20 ^{o}C (Merck, undated) 25 ^{o}C (Kauck and Diesslin, 1951) 22 ^{o}C (Prokop et al., 1989)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	**Experimental** No data **Calculated** No data.	
VII, 7.9	Flash point	3.11	No data found.	
VII, 7.10	Flammability	3.13	No data found.	
VII, 7.11	Explosive properties	3.14	No data found.	
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15	No data found.	
VII, 7.14	Granulometry	3.5		
IX, 7.15	Stability in organic solvents and identity of relevant	3.17		

	degradation products			
IX, 7.16	Dissociation constant	3.21	Dissociation Constants: pKa = 2.80 in 50% aqueous ethanol pKa = 2.5	Brace, 1962 Ylinen et al., 1990
IX, 7.17,	Viscosity	3.22		
	pH value		2.6, 1 g/l (20 ^{o}C)	Merck, 2005, (reliability not assignable)
	Auto flammability	3.12		
	Reactivity towards container material	3.18		
	Thermal stability	3.19		

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

Industrial:

PFOA is used primarily to produce its salts, which are used as essential processing aids in the production of fluoropolymers and fluoroelastomers (68 FR 18626 (4/16/2003, available from http://www.epa.gov.). PFOA is used in fire-fighting applications, cosmetics, grease and lubricants, paints, polishes and adhesives, and in herbicide and insecticide formulations (Moody and Field, 2000). PFOA is also used to make Teflon (DuPont, Teflon, 2006).

General public:

PFOA is used in a variety of commercial applications as refrigerants, surfactants and polymers, and as components of pharmaceuticals, fire retardants, lubricants, adhesives, paints, cosmetics, paper coatings, and insecticides (3M company, 2000).

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

3.2 Self classification(s)

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

See CLH dossier for APFO.

5.2.2 Acute toxicity: inhalation

See CLH dossier for APFO.

5.2.3 Acute toxicity: dermal

See CLH dossier for APFO.

5.2.4 Acute toxicity: other routes

5.2.5 Summary and discussion of acute toxicity

See CLH dossier for APFO.

5.3 Irritation

5.3.1 Skin

See CLH dossier for APFO.

5.3.2 Eye

See CLH dossier for APFO.

5.3.3 Respiratory tract

See CLH dossier for APFO

5.3.4 Summary and discussion of irritation

See CLH dossier for APFO.

5.4 Corrosivity

See CLH dossier for APFO.

5.5 Sensitisation

5.5.1 Skin

See CLH dossier for APFO.

5.5.2 Respiratory system

See CLH dossier for APFO.

5.5.3 Summary and discussion of sensitisation.

See CLH dossier for APFO.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

See CLH dossier for APFO.

5.6.2 Repeated dose toxicity: inhalation

See CLH dossier for APFO.

5.6.3 Repeated dose toxicity: dermal

See CLH dossier for APFO.

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

See CLH dossier for APFO.

5.7 Mutagenicity

5.7.1 In vitro data

See CLH dossier for APFO.

5.7.2 In vivo data

See CLH dossier for APFO.

5.7.3 Human data

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

See CLH dossier for APFO.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

See CLH dossier for APFO.

5.8.2 Carcinogenicity: inhalation

5.8.3 Carcinogenicity: dermal

5.8.4 Carcinogenicity: human data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

See CLH dossier for APFO.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

See CLH dossier for APFO.

5.9.2 Developmental toxicity

See CLH dossier for APFO.

5.9.3 Human data

See CLH dossier for APFO.

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

See CLH dossier for APFO.

5.10 Other effects

Table 2: Exposure of workers

Exposure of workers	Ref.
3M and DuPont have measured the PFOA in serum of occupationally exposed workers from 1995 to 2002. The serum concentration in µg/mL (arithmetic mean) ranged from 0.106 to 6.8 µg/mL in the bio-monitoring data from 3M (Olsen et al., 1998c; 1999; 2000; 2001a and c; 2003 a, b, e and f). In bio-monitoring data from DuPont the serum concentrations in µg/mL (arithmetic mean) ranged from 1.53 to 3.21 µg/mL (DuPont, 2001a and b). 3M and Dupont have conducted several epidemiology and medical surveillance studies of the workers at their plants in various cities of U.S. From these studies it can be concluded that no remarkable health effects that can be directly attributed to PFOA exposure were reported in fluorochemical production workers. However, in a study by Gilliland and Mandel, 1993 a statistically significant association with length of employment in the Chemical Division and prostate cancer mortality was found. An update of this study was conducted in which more specific exposure measures were used, and in this study no significant association for prostate cancer was observed (Alexander, 2001).	Olsen et al., 1998c; 1999; 2000; 2001a and c; 2003 a, b, e and f. DuPont2001a and b. Gilliland and Mandel, 1993; Alexander, 2001

Table 3: Exposure of general population

Exposure of general population	Ref
Data on PFOA levels in the general population include both pooled and individual serum samples. In pooled samples from commercial sources of blood (n=35 lots) the arithmetic mean was 0.003 µg/mL (3M Company, 1999a) and from blood banks, 1998 (n=18 lots, 340-680 donors) the arithmetic mean was 0.017 µg/mL (3M Company, 1999b). In individual samples from the American Red Cross banks, 2000 (n=645) the arithmetic mean was 0.0056 µg/mL and geometric mean 0.0046 µg/mL (Olsen et al., 2002a and 2003d). In elderly people (65-96 years), 2000 (n=238) the geometric mean was 0.0042 µg/mL (arithmetic mean was not reported) (Olsen et al., 2002b and 2004a). In children (2-12 years), 1995 (n=598) the arithmetic mean was 0.0056 µg/mL and the geometric mean was 0.0049 µg/mL (Olsen et al., 2002c and 2004b). In 23 pooled serum samples collected in USA from 1990 through 2002 the median concentration was 0.0116 µg/ml PFOA, and the 90th percentile concentration was 0.0223 µg/ml. In serum samples collected in 2003 from 44 residents in Peru the 90th percentile concentration was 0.0001 µg/ml (Calafat et al., 2006). In a recent study, fifty-seven pooled archived human serum samples were analyzed to assess the time trends as well as influence of age and gender on selected perfluorinated compounds (PFCs) in Norwegian residents. The study comprised determinations of 19 PFCs in serum samples pooled according to year of collection in the period 1976 to 2007. An approximately 9-fold increase in the serum concentrations of PFOA in males age 40-50 years was seen from 1977 to the mid 1990s where the concentration reached a plateau before it started to decrease around year 2000. The PFOA concentration observed in serum in year 2000 (4.5 ng/ml) were approximately two times higher than what was found in 2006 (2.7 ng/ml) (Haug et al. 2009). In a recent Danish study (Joensen et al., 2009), levels of 10 different PFAAs were related to reproductive hormones and semen quality. Serum samples from 105 Danish men (median age, 19 years) were analysed and the median PFOA levels were found to be 4.9 ng/ml.	3M Company, 1999a and b; Olsen et al., 2002 a, b and c; Olsen et al., 2003 d; Olsen et al., 2004a and b. Calafat et al., 2006 Haug et al, 2009; Joensen et al, 2009

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

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Not relevant for this dossier

6.2 Flammability

Not relevant for this dossier

6.3 Oxidising potential

Not relevant for this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier

JUSTIFICATION THAT ACTION IS REQUIRED ON ACOMMUNITY-WIDE BASIS

The assessment of human health hazard for PFOA is based on the human health hazard for APFO since no studies on the human health hazard of PFOA are available. See the CLH dossier for APFO for the assessment of human health hazard for PFOA.

The classification of the salt of PFOA, APFO, was concluded in the former TC C&L group in October 2006. The agreed classification was: Carc. Cat 3; R40, Repr. Cat. 2: R61, T; R48/23, Xn; R48/22, R20/22, Xi; R36. Since this was agreed to be the hamonized classification for PFOA/APFO, we consider it important to includ the complete result of the agreed classification of PFOA/APFO from the discussion in the TC C&L group in Annex VI of the CLP regulation. See Annex I of this report for the dicussion and conclusion og the TC C&L group.

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.

REFERENCES

Alexander BH. 2001. Mortality study of workers employed at the 3M Cottage Grove facility. Final Report, April 2, 2001. Division of Environmental and Occupational Health, School of Public Health, University of Minnesota, US EPA AR226-1030a018.

Boit HG, Editor. 1975. Belstein Handbook of Organic Chemistry. Springer-Verlag, Berlin. 4th Work, Volume 2, Part 2, page 994.

Brace NO. 1962. Long chain alkanoic and alkenoic acids with perfluoroalkyl terminal segments. Journal of Organic Chemistry, 27; 4491-4498.

Calafat AM, Needham LL, Kuklenyik Z, Reidy Jam Tully JS, Aguilar-Villalobos M and Naeher LP. 2006. Perfluorinated chemicals in selected residents of the American continent. Chemosphere, 63; 490-496.

3M Company (Minnesota Mining and Manufactoring Company). 1999a. Letter (dated May 26, 1999) re: TSCA 8(e) Supplemental Notice: Sulfonate-based and carboxylic-based fluorochemicals-Docket Nos. 8EHQ-1180-373; 8EHQ-1180-374; 8EHQ-0381-0394; 8EHQ-0699-373.

3M Company (Minnesota Mining and Manufactoring Company). 1999b. “The science of Organic Fluorochemistry” and “Perfluorooctanesulfonate: current summary of human sera, health, and toxicology data” February 5, 1999. 8EHQ-0299-373.

3M Company. 2000. Voluntary use and exposure information profile for perfluorooctanoic acid and salts. Submission to USEPA, June 8.

Dupont (Haskell Laboratory). 2001a. Letter to Charles Auer from Gerald Kennedy, dated January 25, 2001. FYI-00-001378. US EPA AR226-1000.

Dupont (Haskell Laboratory). 2001b. Letter from Gerald Kennedy re: FYI-010-01378 anf FYI-0301-01378, dated May 29, 2001. . US EPA AR226-1023.

DuPont, Teflon. 2006. Online: http://www.teflon.com/NASApp/teflon/

Gilliland FD and Mandel JS. 1993. Mortality among employees of a perfluorooctanoic acid production plant. J. Occup. Med., 35; 950-954.

Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N and Koizumi A. 2005. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environmental Research, 99; 253-261.

Haug LS, Thomsen C and Becher G. 2009. Time trends and the influence of age and gender on serum concentrations of perfluorinated compounds in archived human samples. Environ. Sci. Technol. 43; 2131-2136.

Joensen UN, Bossi R, Leffers H, Astrup AA, Skakkebæk NE and Jørgensen N. 2009. Do perfluoroalkyl compounds impair human semen quality. Environmental Health Perspectives, 117 (number 6); 923-927.

Kaiser MA, Larsen BS, Kao C-PC and Buck RC. 2005. Vapour pressures of perfluorooctanoic, -nonanoic, -decanoic, undecanoic, and –dodecanoic acids. Journal of Chemical & Engineering Data, 50 (6); 1841-1843.

Kauck EA and Diesslin AR. 1951. Some properties of perfluorocarboxylic acids. Ind. Enf. Chem., 43; 2332-2334.

Kirk-Othmer. 1994. Encyclopaedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V11 (1994) 551.

Merck MSDS online version for PFOA.

Online:
http://www.chemdat.merck.de/pls/pi03/web2.zoom_in?text=807114&screen=110&cid=xcsfs&pg=0&s=&lang=1

Merck KGaA (2005) Material Safety Data Sheet January 20

Moody and Field., 2000 Moody, C. A.; Field, J. A. *Environ. Sci. Technol.* **2000**, *34*, 3864

Olsen GW; Burris JM, Mandel JH and Zobel LR. 1998c. An epidemiologic investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane sulfonate in

male fluorochemical production employees. 3M Company. Final Report. August 22, 1998. US EPA AR226-0030.

Olsen GW. Logan PW, Simpson CA, Hansen KJ, Burris JM, Burlew MM Schumpert JC and Mandel JH. 1999. Fluorochemical exposure assessment of Decatur chemical and film plant employees. 3M Company. Final Report. August 11, 1999. US EPA AR226-0950.

Olsen GW, Burris JM, Burlew MM and Mandel JH. 2000. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem. Tox., 23 (4); 603-620.

Olsen GW, Logan PW, Simpson CA, Burris JM, Burlew MM, Lundberg JK and Mandel JH. 2001a. Descriptive summary of serum fluorochemical levels among employee participants of the year 2000 Decatur fluorochemical surveillance program. . 3M Company. Final Report. March 19, 2001. US EPA AR226-1030a020a.

Olsen GW, Madsen DC, Burris LM and Mandel JH. 2001c. Descriptive summary of serum fluorochemical levels among 236 building employees. 3M Company. Final Report. March 19, 2001. US EPA AR226-1030a020c.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH and Zobel LR. 2002a. Identification of fluorochemicals in human sera. I. American Red Cross adult blood donors. 3M Company. Final Report. February 25, 2002. US EPA 226-1083.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH and Zobel LR. 2002b. Identification of fluorochemicals in human sera. II. Elderly participants of the Adult Changes in Thought Study, Seattle, Washington. 3M Company. Final Report. February 25, 2002. US EPA 226-1084.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH and Zobel LR. 2002c. Identification of fluorochemicals in human sera. III. Pediatric participants in a Group A Streptococci clinical trial investigation. 3M Company. Final Report. February 25, 2002. US EPA 226-1085.

Olsen GW and Mandel JH. 2003a. Descriptive analysis of serum fluorochemical concentrations from Cottage Grove employee participants of the 2002 Medical Surveillance Program. 3M Company. Final Report. US EPA AR226-1353.

Olsen GW and Mandel JH. 2003b. Descriptive analysis of serum fluorochemical concentrations from Decatur employee participants of the 2002 Medical Surveillance Program. 3M Company. Final Report. US EPA AR226-1352.

Olsen GW, Church TR, Miller JP, Burris JM, Hansen KJ, Lundberg JK, Armitage JB, Herron RM, Medhdizadehkashi Z, Nobiletti JB, O'Neill EM, Mandel JH and Zobel LR. 2003d. Perfluorooctanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. Environ. Health Perspect., 111 (16); 1892-1901.

Olsen GW, Burris JM, Burlew MM and Mandel JH. 2003e. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS9 and perfluorooctanoate (PFOA) concentrations and meical surveillance examinations. JOEM 45(3); 260-270.

Olsen GW, Butenhoff JL and Mandel JH. 2003f. Assessment of lipid, hepatic and thyroid function in relation to an occupational biologic limit value for perfluorooctanoate. 3M Company. Final Report. June 9, 2003. US EPA 226-1351.

Olsen GW, Church TR, Larson EB, van Belle G, Lundberg JK, Hansen KJ, Burris JM, Mandel JH and Zobel LR. 2004a. Serum concentrations of perfluorooctanesulfonate and other fluorochemicals in an elderly population from Seattle, Washington, Chemosphere. 54; 1599-1611.

Olsen GW, Church TR, Hansen KJ, Butenhoff JL, Mandel JH and Zobel LR. 2004b. Quantitative evaluation of perfluorooctanesulfonate (PFOS) and other FC's in the serum of children. J. Children's health. 2; 1-24.

Procop HW, Zhou H-J, Xu S-Q, Wu C-H, Liu C-C. 1989. Analysis of the products from the electrochemical fluorination of octanyl chloride. Journal of Fluorine Chemistry, 43 (2); 277-290.

Washburn ST, Bingman TS, Braithwaite SK, Buck RC, Buxton LW, Clewell HJ, Haroun LA, Kester JE, Rickard RW, and Shipp AM (2005). Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles. Environ. Sci. Technol. **39**, 3904-3910 (Supplement).

Ylinen M, Kojo A, Hanhijãrvi H and Peura P. 1990, Deposition of perfluorooctanoic acid in the rat after single and subchronic administration. Bulletin of Environmental Contamination and Toxicology, 44; 46-53.

ANNEX I

Summary record from the TC C&L meeting in Arona, 21-24 March 2006 (ECBI/90/06 Rev.8)

Perfluorooctanic acid (PFOA) [1] and its salts (N003)

Ammonium salt of PFOA, APFO [2]

Sodium salt of PFOA [3]

Potassium salt of PFOA [4]

Silver salt of PFOA [5]

Fluoride acid of PFOA [6]

Methyl ester of PFOA [7]

Ethyl ester of PFOA [8]

(EC number : 206-397-9 [1],

CAS number : 335-67-1 [1]

CAS number : 3825-26-1 [2]

CAS number : 335-95-5 [3]

CAS number : 2395-00-8 [4]

CAS number : 335-93-3 [5]

CAS number : 335-66-0 [6]

CAS number : 376-27-2 [7]

CAS number : 3108-24-5 [8])

Not in Annex 1.

Classification proposal: Carc Cat 3; R 40, Repr Cat 2; R 61, Repr Cat 3; R 62, T; R 48/23, X n; R 20/22, R 48/22, Xi; R 36.

ECBI/18/06 ADD 1

Norway introduced its proposal for the classification of PF0A and its salts by reviewing the various end points and the suggestions for classification.

In Norway's view the classification for acute toxicity and irritancy were straightforward. Classification as Xn; R 48/22 was based on liver toxicity in both mice and rats as demonstrated in several studies. Classification with T; R 48/23 was proposed on the basis of a single study showing liver toxicity at a low doses in rats. The proposal to classify as a carcinogen category 2; R 45 was based on two studies which Norway acknowledged were borderline cases between category 2/3. In the context of fertility Repr Cat 3; R 62 was proposed on the basis of the evidence during two-year carcinogenicity studies where testicular damage had been observed. For developmental toxicity Repr Cat 2; R 61 was proposed based on a two-generation study in which there had been deaths of pups during feeding together with signs of delayed development in the absence of maternal toxicity. Norway made the general point that this substance was related to PFOS for which decisions had already been made in terms of developmental toxicity.

Discussion by the member-states commenced with Germany raising the issue of the substances for which evidence was available. Whilst it was clear that there is a close relationship between the behaviour of the acid and the salts classification should take into account the compound tested. Industry reported that most of the tests had been carried out on the ammonium salt of of PFOA which is the main commercialised product. Both Norway and Industry agreed to provide further information on the identification of the substances used in the different tests.

Notwithstanding the need for further clarification on the above issue the Chair suggested that it would be appropriate to review the various end points and try to reach provisional conclusions on classification.

Irritancy

On this basis TC C&L agreed that Xi; R 36 should be assigned to the ammonium salt on which most of the evidence was based.

Repeat dose toxicity

It was also agreed that Xn; R 48/22 was appropriate for the ammonium salt. In discussion of T; R48/23 industry argued that T was not appropriate. After discussion there was Member States agreement that T; R48/23 would be provisionally assigned. Further comments from industry on this end point will be provided. Meanwhile TC C&L provisionally agreed on Xn; R48/22 and T; R48/23 for the ammonium salt.

Carcinogenicity

In discussion of the carcinogenicity proposal Norway acknowledged that peroxisome proliferation was a possible relevant issue and this would slightly diminish the weight of evidence. However based on work by US EPA Norway had concluded that classification should also take into account the mammary and pancreatic tumours. On the basis of the range of tumours and the number of studies Norway had concluded that Carc Cat 2; R 45 was appropriate. The Chair drew attention to the fact that the original Norwegian proposal was for Carc Cat 3; R 40. Norway was asked to formally present a new proposal. In commenting on the carcinogenicity industry noted that PFOA could be regarded as a mixed inducer and that the observed liver tumours derived from peroxisome proliferation. Industry noted that the Norwegian proposal had stated that the mammary tumours were based on equivocal evidence and argued that there was no increase in the incidence. However Industry acknowledged that the pancreatic tumours could not easily be explained and for this reason agreed to Carc Cat 3; R 40 classification.

Reproductive toxicity

In discussion of reproductive toxicity and the proposal for Repr Cat 3; R 62 Germany commented that the findings were minimal and confined to a few animals with the possibility of age related effects. As a result classification was not appropriate. This position was supported by the United Kingdom and the Netherlands. Denmark indicated a preference for Repr Cat 3 but a majority of The Group agreed no classification for fertility.

On developmental toxicity the Norwegian proposal for Repr Cat 2; R 61 was adjourned.

Conclusion:

It was agreed that further discussion on this substance, and the various end points, will take place at the next meeting.

The meeting was then concluded. ECB thanked the participants for their valuable contributions and reminded of the deadlines for the next meeting.

Summary record from the TC C&L meeting in Arona, 4-5 October 2006 (ECBI/13/07 Rev.2)

Perfluorooctanic acid (PFOA) [1] (N002a)

(EC number : 206-397-9 [1], CAS number : 335-67-1 [1])

Salts of PFOA (N002b):

Ammonium salt of PFOA, APFO [2]

Sodium salt of PFOA [3]

Potassium salt of PFOA [4]

Silver salt of PFOA [5]

Fluoride acid of PFOA [6]

Methyl ester of PFOA [7]

Ethyl ester of PFOA [8]

(CAS number : 3825-26-1 [2]

CAS number : 335-95-5 [3]

CAS number : 2395-00-8 [4]

CAS number : 335-93-3 [5]

CAS number : 335-66-0 [6]

CAS number : 376-27-2 [7]

CAS number : 3108-24-5 [8])

Not in Annex 1.

Classification proposal: Carc Cat 3; R 40, Repr Cat 2; R 61, Repr Cat 3; R 62, T; R 48/23, X n; R 20/22, R 48/22, Xi; R 36.

ECBI/18/06 REV. 1 N, REVISED C&L PROPOSAL FOR PFOA
ECBI/18/06, ADD 1
ECBI/18/06, ADD 2
ECBI/18/06, ADD 3

In **March 2006** it was agreed that further discussion on this substance, and the various end points, will take place at the next meeting.

ECB reported that there was already a discussion going on and that **N** had prepared a new proposal. There was also a document on data that was requested by the MS.

Carcinogenicity:

N started with carcinogenicity and explained the data base. When one compared the historical controls, the substance was a peroxisome proliferater. However compared with a classical peroxisome proliferater the substance in addition increased the liver weight. They stated that with regard to findings of Leydig cell tumours and pancreatic tumors they could not be disregarded to be important for humans.

UK preferred classification with Carc. Cat. 3. Leydig cell tumours in rats did not raise concern. The pancreatic tumors were not really relevant according to them. The whole data base was not robust enough for Carc. Cat 2.

NL and **IT** agreed to the position of the UK.

S and **DK** agreed with N and preferred classification with Carc. Cat. 2 based on the present data.

DE said that there were only tumours found in one species, and the criteria then said that Carc. Cat. 3 should be applied. **FR** agreed to that.

N replied that there were two species. Looking at the tumours for one strain there was a high background but for the other strain not. Also the adenomas cannot be dismissed.

NL asked about the mechanism and said that it it looked like a non-genotoxic mechanism only at high doses.

N replied that little was known about the mechanism and it was of course a borderline case between Carc. Cat. 2 and Carc. Cat. 3.

IND had submitted an abstract about the outcome of a pathology group. There is on-going work on the mechanism. PFOA is a phenobarbital inducer. That is why we have liver growth. The peroxisome proliferation is still under investigation. And also the pancreatic tumours are under discussion. **IND** agreed to Carc. Cat 3.

IND continued and wanted to comment on the nature of the substances. The test material tested 3 M FC143 that contained some branched chain isomers.

ECB replied that the intention would be to treat all substances similar.

NL said that there were some difference and the TC C&L should reflect on whether it would be possible to use the data for the ammonium salt for the other substances.

IND said that the only significant salt is the ammonium salt. We should not get into testing the other salts because it is not worth it.

Reprotoxicity:

N said that there was a new mouse study included in the revised proposal. The effects in the mouse were more severe than those in the rat. There was statistical significant litter absorption. Most of the offspring was alive but at 5 mg did not survive the first day. Delay in eye opening. She quoted the outcome of ECBI/18/06 Add. 3. The renal clearance in mice is lower in mice than in rats and in humans its even lower. That is why the mouse study should be considered.

UK said that the findings were confounded by marked maternal toxicity. They would therefore support Cat 3 for developmental effects.

S supported N as the maternal toxicity was not the reason for the findings. **DK** agreed to this.

DE said that the mouse reacts with absorptions to maternal toxicity and there is also effects at low doses were there is no maternal toxicity and the pup mortality is increased. The pup mortality is very rare in mouse. They therefore ended up with classification in Category 2

IND said the effects in mice were compromised by maternal toxicity.

NL agreed with DE and supported N because of the effects at the low doses.

UK pointed out that maternal toxicity was seen at all doses.

The **TC C&L** on the reasoning referred to above and supported by a majority of the experts agreed to Category 2 for development R61

At the last meeting co classification for fertility had already been agreed.

Acute Toxicity:

ECB said that Xn; R20/22 was agreed already for the ammonium salt.

NL said that for inhalation for ammonium and sodium salt would probably be possible to read across but for silver and fluoride acid and for the esters listed the inhalation route could be different.

FIN said that probably some of the substances were not on the market and it would be necessary only to classify those that were.

DE thought it was better to cover the toxicology for similar compounds as the market was changing and new similar products very well could be introduced.

ECB asked whether there should be split the entries for different compounds.

IND reported about the use pattern. The again stressed that the main use was ammonium salt. They thought it might be convenient to read-across to inhalation toxicity in this case as there was no intention from IND to conduct any further studies on the different compounds listed in the currently drafted entry.

ECB summarised that the TC C&L then would agree to read across inhalation toxicity. **NL** stressed that it should be minuted that the read-across was made out of practical reasons as referred to above and this should not be used as an example for read-across.

The acute toxicity by oral route was agreed without further discussion for all salts.

Repeated dose Toxicity:

IND said that there was an inhalation study where mortality occurred. They said that this would trigger R48/20.

N reported the data again and said that R48/23 was warranted.

DE agreed to the N proposal based on the presented data.

IND said that this was a question of interpretation. There was some uncertainty. The study had to be transformed as there was an outlier.

The **TC C&L** agreed to T; R48/23 as suggested by N. They also agreed to Xn; R48/22 agreed based on the N proposal.

S also wanted to discuss R48/24.

N did not suggest classification for dermal route since they thought there was not enough data. But they volunteered to have an additional look at the data available. Perhaps the data would rather justify R48/21.

IND said that the substance was absorbed through rat skin but this was not demonstrated in humans. There were significant differences. **IND** would send in data on this during the Follow-up period.

Irritancy:

The TC C&L agreed to Xi; R36 without further comments.

Conclusion :

The TC C&L agreed to the following classification proposal: Carc. Cat. 3; R40 - Repr. Cat 2; R61 - T; R48/23 - Xn; R20/22 -Xn; R48/22 - Xi; R36, further the following labeling was agreed: Symbol: T; R-phrases: 61-20/22-36-40-48/22-48/23 and S-phrases: 53-45.

All substances as listed in the draft entry were thereby classified but the read across was done based on pragmatism as no further data would be assumed to be available for these substances. The read across had not been discussed on the basis of different physical chemical properties and structure relationships between the different substances considered.