S I D S

D o s s i e r

Existing Chemical	: ID: 3825-26-1
CAS No. Substance	: 3825-26-1
name	: Ammonium Perfluorooctanoate

Producer related part

Company	: E. I. du Pont de Nemours and Company
Creation date	: 07.09.2005

Substance related part

Company	: E. I. du Pont de Nemours and Company
Creation date	: 07.09.2005
Status	:
Memo	: OECD HPV Chemical Programme, SIDS Dossier, approved at SIAM 22 (18-21 April 2006)
Printing date	
Revision date	: 16.01.2007
Date of last update	:
	: 16.01.2007
Number of pages	
	: 201
Chapter (profile)	
Reliability (profile)	: Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Flags (profile)	: Reliability: without reliability, 1, 2, 3, 4
	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	E. I. du Pont de Nemours and Company
Contact person	:	
Date	:	
Street	:	1007 Market Street
Town	:	19898 Wilmington, Delaware
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

07.09.2005

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type	:	manufacturer
Name of plant	:	DuPont
Street	:	
Town	:	
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

22.12.2006 (551)

Type	:	manufacturer
Name of plant	:	Daikin
Street	:	
Town	:	
Country	:	Japan
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

22.12.2006 (551)

Type	:	manufacturer
Name of plant	:	Miteni
Street	:	
Town	:	
Country	:	Italy
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	

Email	:	
Homepage	:	

22.12.2006 (551)

Type	:	
Name of plant	:	Name is not available
Street	:	
Town	:	
Country	:	other: China
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

22.12.2006 (551)

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Ammonium Pentadecafluorooctanoate
Smiles Code	:	
Molecular formula	:	
Molecular weight	:	431 g/mol
Petrol class	:	

21.12.2006

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	solid
Purity	:	= 96.5 - 100 % w/w
Colour	:	Light colored powder
Odour	:	Slight odor
Remark	:	These data refer to a 3M product FC-143 Fluorad Brand Fluorochemical Surfactant.

19.01.2006 (14)

1.1.2 SPECTRA

Type of spectra	:	UV
Remark	:	no UV absorption in water < 290 nm (acid) - Ref. Hori et al., 2005 (Need more info)
Test substance	:	PFOA (>95%, Wako Pure Chemical Industries)
Reliability	:	(2) valid with restrictions

1.2 SYNONYMS AND TRADENAMES

APFO

07.09.2005 (237)

C-8

07.09.2005 (237)

FC-143

13.10.2005 (237)

Information on PFOA

Remark : APFO is the ammonium salt of perfluorooctanoic acid (PFOA), CAS # 335-67-1. PFOA is also named:

n-Perfluorooctanoic acid
Pentadecafluoro-n-octanoic acid
Pentadecafluorooctanoic acid
Perfluorocaprylic acid
Perfluoroheptanecarboxylic acid

22.12.2006

11.10.2005

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 21615-47-4
EC-No : 244-479-6
EINECS-Name : ammonium undecafluorohexanoate
Molecular formula :
Value : = 0 - 1.5 % w/w

Remark : These data refer to a 3M product FC-143 Fluorad Brand Fluorochemical Surfactant.

10.01.2006 (14)

Purity : typical for marketed substance
CAS-No : 6130-43-4
EC-No : 228-098-2
EINECS-Name : ammonium perfluoroheptanoate
Molecular formula :
Value : = 0 - 1 % w/w

Remark : These data refer to a 3M product FC-143 Fluorad Brand Fluorochemical Surfactant.

10.01.2006 (14)

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :

Molecular formula :
Value : 0 - 1 % w/w

Remark : These data refer to a 3M product FC-143 Fluorad Brand Fluorochemical Surfactant.
Test substance : ammonium heptadecafluorononanoic acid
10.01.2006 (14)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Remark : By 2002, the principal worldwide APFO manufacturer by the ECF process, 3M, discontinued external sales and ceased production leaving only a number of relatively small producers in Europe and in Asia (OECD, 2004). New APFO production capacity based on >99% pure perfluorooctyl iodide commenced in the U.S. by DuPont in late 2002 . At the time of shut down, 3M listed their APFO capacity at 227 metric tons per year. DuPont's capacity was given as 136 metric tons per year at the time of start up.
22.12.2006 (156) (462) (576)

1.6.1 LABELLING

Labelling : other, as in legislation: Denmark Advisory Risk Phrase
Specific limits : no
Nota : , ,
R-Phrases : (22) Harmful if swallowed
(52) Harmful to aquatic organisms
(53) May cause long-term adverse effects in the aquatic environment
S-Phrases :

Test substance : APFO
10.01.2006 (77)

Labelling : other, as in legislation: Germany List of Water-Endangering Substances [WGK ID # = 1411]
Specific limits : no

Test substance : APFO
10.01.2006 (77)

Labelling Specific : other, as in legislation: Japan
limits : yes

Result : Chemical is subject to regulation if present at 1.0 wt% or more.
Test substance : APFO
10.01.2006 (77)

Labelling Specific : other, as in legislation: Massachusetts Right-to-Know Substances List
limits : no

Test substance : APFO
10.01.2006 (77)

Labelling Specific : other, as in legislation: Minnesota Hazardous Substances List
limits : yes

Result : Skin Designation Applies
Test substance : APFO
10.01.2006 (77)

1.6.2 CLASSIFICATION

Classified : provisionally by manufacturer/importer
Class of danger :
R-Phrases Specific :
limits :

Remark : FC-143 is not listed by DOT. The 3M data for acute oral toxicity indicates FC-143 should not be regulated. However, DuPont inhalation data indicates an LC50, extrapolated to one hour, to be 3.92 mg/L, and thus it would appear FC-143 would be an 6.1 Packaging Group 3. Therefore, 3M lists FC-143 under DOT/ICAO/IMO, as: "Poisonous 6.1 (Liquid or Solid) PG III".
Test substance : APFO
10.01.2006 (237)

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Polymers industry

08.09.2005

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : From 1947, the electrochemical fluorination (ECF) process was used worldwide to manufacture the majority of APFO [80-90% in 2000] (Simons, 1949). The largest production sites were in the United States (the ECF process stopped in 2002) and Belgium (production stopped in 2002), the next largest in Italy, and small scale producers were located in Japan. In 2002, DuPont and Daikin committed to selling APFO only for use in the fluoropolymer industry (SPI, 2002).

The remaining 10-20% of APFO was manufactured from about 1975 to present by direct oxidation of perfluorooctyl iodide at one site in Germany (production stopped in 2004), at least one site in Japan, and by DuPont in the USA. APFO has been mostly used in making fluoropolymers. Additional limited research quantity production, use and disposal have taken place in numerous academic and industrial locations worldwide over the past fifty years as indicated by patents and papers in the scientific literature (Prevedouros et al., 2006; EPA Docket's EPA-HQ-OPPT-2003-0012, EPA-

HQ-OPPT-2004-0112, and EPA-HQ-OPPT-2004-0113).
22.12.2006 (254) (255) (256) (503) (554) (576)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value : .01 mg/m3

Remark : skin notation
13.10.2005 (67)

Type of limit : other: In Argentina, Bulgaria, Columbia, Jordan, Korea, Singapore, and Vietnam
Limit value : .01 mg/m3

Remark : skin notation
25.10.2005 (507)

Type of limit : other: Biological limit value for PFOA in serum
Limit value : 5 other: ppm

Result : A biological limit value (BLV) for PFOA in the serum of workers has been established by 3M. The BLV represents the best scientifically-based estimate of a concentration of PFOA in a biological fluid (serum) that, if present, even on a chronic basis, is not expected to correlate with a risk of adverse health effects in workers.
Test substance : PFOA
22.12.2006 (531)

Type of limit Limit value : other: DuPont Acceptable Exposure Limit (AEL), 8-hour TWA
: .01 mg/m3

Remark : skin notation
13.10.2005 (237)

Type of limit Limit value : other: DuPont Community Exposure Guideline (CEG), air
: .3 µg/m3

13.10.2005 (237)

Type of limit Limit value : other: DuPont Community Exposure Guideline (CEG), water
: 1 µg/l

13.10.2005 (237)

Type of limit : other: Occupational Exposure Limit (OEL) for Australia, Belgium, New Zealand, and Quebec
Limit value : .1 mg/m3

Remark : skin notation
13.10.2005 (77)

Type of limit : other: Occupational Exposure Limit (OEL) for British Columbia, California, Denmark, Indonesia, Ireland, Italy, Malaysia, The Netherlands, and Spain
Limit value : .01 mg/m3

Remark : skin notation
13.10.2005 (77)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : TSCA
Additional information :

13.10.2005 (237)

Type : DSL
Additional information :

13.10.2005 (237)

Type : EINECS
Additional information : 223-320-4

13.10.2005 (237)

Type : ECL
Additional information : KE-27884

13.10.2005 (237)

Type : ENCS
Additional information : ENCS 2-1195

13.10.2005 (237)

Type : AICS
Additional information :

13.10.2005 (237)

Type : CHINA
Additional information :

13.10.2005 (237)

Type : PICCS
Additional information :

13.10.2005 (237)

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Remark : no degradation/transformation during usual application
22.12.2006

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Environmental exposure from:

Production and use of APFO

APFO residue in products (fluoropolymers, fluoroelastomers) manufactured with the help of APFO

APFO impurities in products not made with the help of APFO
biotic and abiotic degradation of other perfluorinated substances to PFOA

22.12.2006 (503)

1.11 ADDITIONAL REMARKS

Memo : Ammonium Perfluorooctanoate (APFO) is the ammonium salt of perfluorooctanoic acid (PFOA, CAS # 335-67-1). PFOA is also included in this dataset. When PFOA is the tested substance, it will be indicated in the TS field.

12.01.2006

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : 157 - 165 °C
Sublimation :
Method :
Year : 1984
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Decomposition starts above 105°C
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment
22.12.2006 (414)

Value : 130 °C
Decomposition : yes, at °C
Sublimation :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Documentation insufficient for assessment
20.01.2006 (5)

Value : 130 °C
Sublimation : yes
Method :
Year : 1980
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Documentation insufficient for assessment
20.01.2006 (285)

Value : 54.3 °C
Sublimation : yes
Method :
Year :
GLP :
Test substance : other TS

Result : Sublimination Point = 40°C.
Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
20.01.2006 (412)

Value : 44 - 56.5 °C
Sublimation :
Method :
Year :
GLP :
Test substance : other TS

Remark : Range from 6 references
Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
22.12.2006 (83)

Sublimation : yes
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
20.01.2006 (346)

2.2 BOILING POINT

Decomposition : yes
Method :
Year : 1984
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment
22.12.2006 (414)

Value : 188 °C at 1013.8 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.01.2006 (412)

Value : 189 °C at 981 hPa
Decomposition :
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
20.01.2006 (355)

2.3 DENSITY

Type : density

Value : .6 - .7 g/cm³ at 20 °C
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Data from handbook or collection of data
12.01.2006 (285)

Type : density
Value : 1.792 g/cm³ at 20 °C
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.12.2006 (378)

Type : density
Value : 1.8 g/cm³ at 20 °C
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (4) not assignable
Secondary literature
22.12.2006 (440)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .000081 hPa at 20 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
12.01.2006 (623)

Value : .00044 hPa at 40 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
12.01.2006 (623)

Value : .0025 hPa at 60 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
12.01.2006 (623)

Value : .014 hPa at 80 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (623)

Value : .037 hPa at 90.1 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : .095 hPa at 99.7 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : .085 hPa at 100 °C
Decomposition :
Method : other (calculated)

Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (623)

Value : .21 hPa at 109.4 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : .44 hPa at 119.2 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : .51 hPa at 120 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (623)

Value : 3.08 hPa at 140 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (623)

Value : 7.999 hPa at 150 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : 19.02 hPa at 160 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (623)

Value : 19.998 hPa at 160 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : 29.331 hPa at 165 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Gas Saturation Method (USEPA OPPTS 830.7950)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
22.12.2006 (623)

Value : 30.02 hPa at 165 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Calculated vapor pressures for APFO were based on the fitted Antoine equation: Log (v.p. mmHg) = -18.3324 + 502.464/T(°K) + 0.04231 x T(°K).
Reliability : (2) valid with restrictions

Accepted calculation method

22.12.2006 (623)

Value : .023 hPa at 20 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : .042 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint

22.12.2006 (346) (503)

Value : 1.28 hPa at 59.3 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 1.68 hPa at 62.4 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : .22 hPa at 40 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 1.37 hPa at 60 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 2.31 hPa at 66.6 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 3.61 hPa at 72.6 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 5.81 hPa at 79 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 6.15 hPa at 80 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 9.6 hPa at 86.6 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 16.02 hPa at 94.9 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 21.55 hPa at 100 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 26.9 hPa at 103.9 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 45.91 hPa at 114 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 62.38 hPa at 120 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 76.91 hPa at 124.4 °C
Decomposition :

Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 130.66 hPa at 136.1 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 155.35 hPa at 140 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 221.6 hPa at 148.6 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 342.91 hPa at 160 °C
Decomposition :

Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 372.46 hPa at 162.2 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 639.79 hPa at 177.8 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

Value : 686.16 hPa at 180 °C
Decomposition :
Method : other (calculated)
Year : 2005
GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 940.74 hPa at 190 °C
Decomposition :
Method : other (calculated)
Year : 2005

GLP :
Test substance : other TS

Method : Calculated vapor pressures for PFOA were based on the fitted Antoine equation: Ln (v.p. psia) = 12.79654 - 3388.046/(T(°K) - 130.441).
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2006 (623)

Value : 965.01 hPa at 190.8 °C
Decomposition :
Method : other (measured)
Year : 2005
GLP :
Test substance : other TS

Method : Dynamic measurement method according to L. Scott (1986). Determination of activity coefficients by accurate measurement of boiling point diagram. Fluid Phase Equilib., 26:149-163 (as cited in Kaiser et al., 2005).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (346) (623)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : at °C
pH value :
Method : other (measured)
Year :
GLP : no data
Test substance : other TS

Result : In aqueous solutions, individual molecules of PFOA anion loosely associate on the water surface and partition between the air/water interface. Several reports note that PFOA salts self-associate at the surface, but with agitation they disperse and micelles form at higher concentrations. Water solubility has been reported for PFOA, but it is unclear whether these values are for a microdispersion of micelles, rather than true solubility. Due to these same surface-active properties of PFOA, and the test protocol for the OECD shake flask method, PFOA is anticipated to form multiple layers in octanol/water, much like those observed for PFOS. Therefore, an n-octanol/water partition coefficient cannot be determined.
Test substance : PFOA
Reliability : (4) not assignable
Secondary literature

12.01.2006 (116) (241) (553)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 50 vol% at °C
pH value :
concentration : at °C

Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Room Temperature
Reliability	:	(4) not assignable Secondary literature

13.01.2006 (264)

Solubility in	:	Water
Value	:	at °C
pH value	:	4 - 7
concentration	:	2 vol% at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable Secondary literature (Material Safety Data Sheet)

13.01.2006 (14)

Solubility in	:	Water
Value	:	> 500 g/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Reliability	:	(4) not assignable Documentation insufficient for assessment

19.01.2006 (5) (550)

Solubility in	:	Water
Value	:	3.4 g/l at 20 °C
pH value	:	2.6
concentration	:	1 g/l at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	1.5 at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	2005
GLP	:	

Test substance : other TS

Test substance : PFOA
Reliability : (4) not assignable
Secondary literature (Material Safety Data Sheet)
20.01.2006 (439) (450)

Solubility in : Water
Value : 3.4 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment
20.01.2006 (440)

Solubility in : Water
Value : 4.1 g/l at 22 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Test substance : Perfluorooctanoate (PFO)
Reliability : (4) not assignable
Secondary literature
20.01.2006 (504)

Solubility in : Water
Value : 9.5 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : Original reference: Saturated solution at 25 deg Celsius was measured to be 0.023 molar.
Test substance : Perfluorooctanoate (PFO)
Reliability : (2) valid with restrictions
Scientifically acceptable
20.01.2006 (355)

Solubility in : Organic Solvents
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : soluble (1000-10000 mg/L)

Stable	:	
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Soluble in acetone and ethanol (1000-10,000 mg/L)
Reliability	:	(4) not assignable Secondary literature (Material Safety Data Sheet)

20.01.2006 (14)

Solubility in	:	Organic Solvents
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Remark	:	Solubility in Heptane, Toluene: 0 g/l Solubility in Methanol, Acetone: > 500 g/l
Test substance	:	PFOA
Reliability	:	(4) not assignable Secondary literature

22.12.2006 (5)

2.6.2 SURFACE TENSION

Test type	:	
Value	:	15.2 mN/m at °C
Concentration	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS
Test substance	:	PFOA
Reliability	:	(2) valid with restrictions Data from handbook or collection of data

13.01.2006 (379)

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result	:	non flammable
Method	:	
Year	:	1980
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Documentation insufficient for assessment

12.01.2006 (285)

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : 3.66
Method : other
Year : 2003
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Original reference not yet available

12.01.2006 (227)

Method :
Year :
GLP :
Test substance : other TS

Result : Acid-dissociation Constant = 1.5 to 2.8 as pKa.
Test substance : PFOA
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint

12.01.2006 (264) (380)

Acid-base constant : 2.5
Method :
Year :
GLP :
Test substance : other TS

Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

12.01.2006 (280) (650)

Method :
Year :
GLP :
Test substance : other TS

Remark : The low reported pKa values of PFOA indicate that both PFO and PFOA are present in the environment. PFO and PFOA have different physical-chemical properties and environmental partitioning behavior. At pH 7, only 3-6 in 100,000 molecules are PFOA, with the remaining being PFO. At pH 4, about 6% will be PFOA molecules.
Test substance : PFOA and Perfluorooctanoate (PFO)
Reliability : (4) not assignable
Documentation insufficient for assessment

12.01.2006 (503)

Acid-base constant : 2.8
Method :
Year :
GLP :
Test substance : other TS

Result : Brace measured the pKa of PFOA as 2.80 plus or minus 0.03 at 25°C using pH titration of 0.005M PFOA with a titrant of 0.1 N sodium hydroxide in 50% aqueous ethanol.
Test substance : PFOA
Reliability : (2) valid with restrictions
Scientifically acceptable

19.01.2006 (106)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Critical Micelle Concentration (CMC)

Result : CMC for PFOA = 8.7-9.0 mmoles/L [3.6-3.7 g/L].
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
12.01.2006 (379)

Memo : Critical Micelle Concentration (CMC)

Result : CMC for Perfluorooctanoate = 3.7 g/L.
Reliability : (4) not assignable
Documentation insufficient for assessment
12.01.2006 (453)

Memo : Krafft Point (the limit at which compounds cease to be singly dispersed and begin to form micelles)

Result : 20°C for Perfluorooctanoate.
Reliability : (4) not assignable
12.01.2006 (453)

3.1.1 PHOTODEGRADATION

Type : other: (simulated sunlight)
Light source : other: (Suntest CPS+ or Suntest XLS+)
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 2001
GLP : no
Test substance :

Method : To test for indirect photolysis, a synthetic light source was used to initiate radical formation in three separate matrices: a synthetic humic matrix, a hydrogen peroxide rich matrix, and an iron containing matrix (as Fe2O3). The method is consistent with OPPTS: 835.5270 "Indirect Photolysis Screening Test" and OECD Draft Document "Phototransformation of Chemicals in Water - Direct and Indirect Phototysis", August 2000.
Result : Degradation of PFOA was not observed in any matrix outside of the experimental precision of the analytical methodology. Mass balance for the degradation study was 100 plus or minus 10% under all experimental conditions. A minimum half-life for PFOA was calculated to be 349 days or more.
Test substance : PFOA (95% purity)
Reliability : (1) valid without restriction
Comparable to guideline study

22.12.2006 (54)

Type : other
Light source : other: Suntest CPS+ or Suntest XLS+
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 2001
GLP : no
Test substance :

Method : In the present investigation, an artificial light source was used to study the direct photolysis reactions of PFOA. The method is consistent with OPPTS: 835.5270 "Indirect Photolysis Screening Test" and OECD Draft Document "Phototransformation of Chemicals in Water - Direct and Indirect Phototysis", August 2000.
Result : Direct photolytic decomposition of PFOA was not observed based on loss of starting material nor were any of the predicted degradation products detected above their LOQ (see below).

[The limit of quantitation (LOQ) is equal to the concentration of lowest standard in the calibration curve that has an area greater than or equal to four times the solvent blanks and possessing a residual less than 25% of the actual value].
Test substance : PFOA (>95% purity)
Reliability : (1) valid without restriction
Comparable to guideline study

22.12.2006 (54)

Type : other
Light source Light : Xenon lamp
spectrum : nm

Relative intensity : based on intensity of sunlight
Conc. of substance : 1.35 mmol/l at °C
DIRECT PHOTOLYSIS
Halflife t1/2 :
Degradation : = 89.5 % after 72 hour(s)
Quantum yield :
Deg. product :
Method : other (measured)
Year : 2004
GLP : no data
Test substance :

Method : The decomposition of PFOA in water by UV-visible light irradiation, by H202 with UV-visible light irradiation, and by a tungstic heteropolyacid photocatalyst was examined.
Result : 89.5% of the initial PFOA decomposed after 72 hours of irradiation of PFOA under 0.48 mPa of oxygen at room temperature with the formation of F-, CO2, and short-chain perfluorocarboxylic acids. Under similar conditions, the presence of a tungstic heteropolyacid photocatalyst, led to complete PFOA decomposition after 24 hours of irradiation. Compared to direct photolysis, H2O2 was less effective in PFOA decomposition [35.5% versus 44.9% in 24 hours]. When the irradiation was conducted in the presence of 0.48 mPa of argon, the amount of PFOA decomposed was slightly decreased [43.2% versus 44.9% in oxygen] whereas the amount of F- and, especially, CO2 relevantly decreased. This suggests that oxygen plays an important role, probably not in the first PFOA decomposition step [C-C bond cleavage between C7F15 and COOH] but in the subsequent steps that produce F- and CO2.
Test substance : >95% PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (325)

Type : other
Light source : Xenon lamp
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Conc. of substance : .2 mg/l at °C
Deg. product :
Method : other (measured)
Year : 2005
GLP : no data
Test substance :

Method : Photochemical decomposition of persistent perfluorocarboxylic acids (PFCAs) in water by use of persulfate ion [S208(2-)] was examined.
Remark : Solvent is 70/30 methanol/aqueous NaH2PO4
Result : PFOA was completely decomposed by a photochemical system with 50 mM persulfate ion and 4 hours of irradiation from a 200 watt xenon-mercury lamp. When the solution was irradiated in the absence of persulfate ion [direct photolysis], PFOA decomposition, F- formation, and CO2 formation, all markedly decreased compared to those in the presence of persulfate ion [16.8% versus 100%]. When the irradiation with persulfate ion was conducted in the presence of 0.48 mPa of argon, the reaction yields of PFOA decomposition, F- formation, and CO2 formation were similar to those under oxygen. Thus, the oxygen gas in the reaction system does not play a significant role in the PFOA decomposition system.
Test substance : PFOA (>95% purity)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (326)

Type : water
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : OH
Conc. of sensitizer :
Rate constant : cm^3/(molecule*sec)
Degradation : % after
Deg. product : yes
Method : other (measured)
Year : 2005
GLP : no data
Test substance :

Method : The 8:2 fluorotelomer alcohol [1H,1H,2H,2H-perfluoro-1-decanol] (8:2 FTOH) was photodegraded in aqueous hydrogen peroxide solutions, synthetic field water (SFW) systems, and Lake Ontario (Canada) water samples.
Result : 8:2 Telomer alcohol was found to undergo indirect photolysis, with the data suggesting that the hydroxyl radical was the main degradation agent and that nitrate promoted photolysis whereas dissolved organic carbon inhibited it. The half-lives of 8:2 FTOH were 0.83 h (10 mM H2O2), 38.0 h (100 microM H2O2), 30.5 to 163.1 h (synthetic field water systems), and 93.2 h (Lake Ontario). No significant loss of the parent compound by direct photolysis could be observed. The major monitored products were the 8:2 fluorotelomer aldehyde, the 8:2 fluorotelomer acid (8:2 FTCA), and perfluorooctanoate (PFOA); the minor monitored products were the 8:2 fluorotelomer unsaturated acid (8:2 FTUCA) and perfluorononanoate (PFNA). The intermediates, 8:2 FTCA and 8:2 FTUCA, were photodegraded to verify the degradation pathway, and a mechanism for the photolysis was proposed whereby the end products of the photolysis pathway were PFOA (major) and PFNA (minor).
Test substance : 8:2 Telomer alcohol (1H,1H,2H,2H-Perfluoro-1-decanol)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

22.12.2006 (272)

Type : other: (simulated sunlight)
Light source : other: (GE 4-40BL fluorescent black light)
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Conc. of substance : 50 mg/l at °C
Deg. product :
Method : other (measured)
Year : 1979
GLP : no
Test substance :

Method : This study investigated the possible photodegradation of APFO in distilled water on exposure to simulated sunlight. The study was conducted essentially as recommended by EPA (see Federal Register, Volume 43, No. 132, Monday, July 10, 1978 for method).
Remark : other light spectrum max output at about 360 nm, essentially no output below 300 nm
Result : Photolyzate samples were collected after irradiation intervals of 0, 1, 3, 7, 15, and 30 days. No photodegradation of the test substance was detected in this study. Essentially the same analysis results were obtained for the 30-day photolyzate sample and the 0-day sample (no photoproducts

formed).

Test substance : 14C labeled (358 dpm/ug) APFO, mixture of 96.5-100% APFO, 0-3.5% C6, C7 and C9 perfluoro analogue compounds

Reliability : (2) valid with restrictions
(2) Study well documented, meets generally accepted scientific principles, acceptable for assessment

22.12.2006 (31)

Type : other
Light source : other: GE F15T8BL fluorescent black lamps
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured): see Ellis DA et al. (2003) Environ. Sci. Technol, 37:3816-3820.
Year : 2006
GLP : no
Test substance :

Method : Perfluorooctanesulfonamides [C8F17SO2N(R1)(R2)] are present in the atmosphere and may, via atmospheric transport and oxidation, contribute to perfluorocarboxylates (PFCA) and perfluorooctanesulfonate (PFOS) pollution in remote locations. Smog chamber experiments with the perfluorobutanesulfonyl analogue N-ethyl perfluorobutanesulfonamide [NEtFBSA; C4F9SO2N(H)CH2CH3] were performed to assess this possibility.

Result : By use of relative rate methods, rate constants for reactions of NEtFBSA with chlorine atoms (296K) and OH radicals (301K) were determined to be kCL) = (8.37 +/- 1.44) x 10E-12 and kOH = (3.74 +/- 0.77) x 10E-13 cm3/molecule/s, indicating OH reactions will be dominant in the troposphere. Simple modeling exercises suggest that reaction with OH radicals will dominate removal of perfluoroalkanesulfonamides from the gas phase (wet and dry deposition will not be important) and that the atmospheric lifetime of NEtFBSA in the gas phase will be 20-50 days, thus allowing substantial long-range atmospheric transport. Liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis showed that the primary products of chlorine atom initiated oxidation were the ketone C4F9SO2N(H)COCH3; aldehyde 1, C4F9SO2N(H)CH2CHO; and a product identified as C4F9SO2N(C2H5O)- by high-resolution MS but whose structure remains tentative. Another reaction product, aldehyde 2, C4F9SO2N(H)CHO, was also observed and was presumed to be a secondary oxidation product of aldehyde 1. Perfluorobutanesulfonate was not detected above the level of the blank in any sample; however, three perfluoroalkanecarboxylates (C3F7CO2-, C2F5CO2-, and CF3CO2-) were detected in all samples. Taken together, results suggest a plausible route by which perfluorooctanesulfonamides may serve as atmospheric sources of PFCAs, including perfluorooctanoic acid.

Test substance : N-ethyl perfluorobutanesulfonamide
Reliability : (2) valid with restrictions

22.12.2006 (427)

Type : other
Light source : other: 22 (GE F15T8BL) fluorescent black lamps
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 2006
GLP : no
Test substance :

Method : Smog chamber, relative rate method, reaction with OH radicals (296K) in a

140-liter borosilicate glass reactor interfaced to a fourier transform infrared (FTIR) spectrometer +offline GC-MS and LC-MS/MS analysis. OH radical experiments initial gas mixture concentrations: were 4-9 mTorr of NEtFBSA, 1-3 mTorr of the reference compound (C2H2), and 175-220 mTorr of CH3ONO in 700 Torr of air diluent.

Result : k(OH + NMeFBSE) = (5.8 +/- 0.8) x 10E-12 cm3/molecule/s in 750 Torr of air diluent at 296K. The atmospheric lifetime of NMeFBSE is determined by reaction with OH radicals and is approximately 2 days. Degradation products were identified by in situ FTIR spectroscopy and offline GC-MS and LC-MS/MS analysis. The primary carbonyl product C4F9SO2N(CH3)CH2CHO, N-methyl perfluorobutane sulfonamide (C4F9SO2NH(CH3)), perfluorobutanoic acid (C3F7C(O)OH), perfluoropropanoic acid (C2F5C(O)OH), trifluoroacetic acid (CF3C(O)OH), carbonyl fluoride (COF2), and perfluorobutane sulfonic acid (C4F9SO3H) were identified as products. A mechanism involving the addition of OH to the sulfone double bond was proposed to explain the production of perfluorobutane sulfonic acid and perfluorinated carboxylic acids in yields of 1 and 10%, respectively. The gas-phase N-dealkylation product, N-methyl perfluorobutane sulfonamide (NMeFBSA), has an atmospheric lifetime (>20 days) which is much longer than that of the parent compound, NMeFBSE. Accordingly,the production of NMeFBSA exposes a mechanism by which NMeFBSE may contribute to the burden of perfluorinated contamination in remote locations despite its relatively short atmospheric lifetime. Using the atmospheric fate of NMeFBSE as a guide, it appears that anthropogenic production of N-methyl perfluorooctane sulfonamidoethanol (NMeFOSE) contributes to the ubiquity of perfluoroalkyl sulfonate and carboxylate compounds in the environment.

Test substance : N-methyl perfluorobutanesulfonamidoethanol
Reliability : (2) valid with restrictions
22.12.2006 (142)

Type : other: calculation
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (calculated)
Year : 2006
GLP :
Test substance :

Method : Calculations were made using a three-dimensional global atmospheric chemistry model (IMPACT).

Result : n-C8F17CH2CH2OH degrades in the atmosphere to give perfluorooctanoic acid (PFOA) and other perfluorocarboxylic acids (PFCAs). Molar yields of PFOA depend on location and season, are in the range of 1-10%, and are of the correct order of magnitude to explain the observed levels in Arctic fauna.

Test substance : 8:2 Fluorotelomer Alcohol
Reliability : (2) valid with restrictions
Accepted calculation method
22.12.2006 (620)

Type : other
Light source : other: UV Lamps
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 2003
GLP : no
Test substance :

Method : Kinetic rate constants of TFP and TDO with OH radicals measured in a 150 L Teflon bag irradiated by UV lamps. OH radicals produced by photolysis of H2O2 at 254 nm. The time profiles of reactant consumption and product formation were obtained by Fourier Transformed Infrared (FTIR) Spectroscopy and Gas phase Chromatography coupled with a Flame Ionisation Detection (GC/FID). FTIR analysis was made in a Nicolet White gas cell of 2 L and 25 cm length with an optical multipath of 10 m. Analysis was at atmospheric pressure with 2 L samples taken from the reaction mixture for each FTIR analysis. For GC/FID analysis a smaller volume of around 0.1 L was sampled from the chamber and flushed into the GC/FID system. A mass spectrometer coupled to the GC was used to follow the time evolution of the ionized fragments and gives qualitative information about the products formed. Concentration time profiles of reactants were obtained by FTIR or GC analysis.

Result : Measured rate constant for
OH + TFP: k = (1.06 ± 0.10) x 10E-12 cm3/molecule/s
OH + TDO: k = (0.99 ± 0.18) x 10E-12 cm3/molecule/s

As nearly the same values were obtained for TFP and TDO, this indicates that the nature of the perfluorinated group has no influence on the reactivity of the alcohol. Therefore, the above value of the rate constant can be recommended for the reaction OH + 8-2 telomer alcohol: k = (1.0 ± 0.2) x 10E-12 cm3/molecule/s at 298K.

Test substance : trifluoropropanol (TFP); tridecafluoro octanol (TDO)

22.12.2006 (407)

Type : water
Light source : other: Suntest CPS+ or Suntest XLS+ lamp
Light spectrum : 290 - 800 nm
Relative intensity : 680 based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : other
Conc. of sensitizer :
Rate constant : cm^3/(molecule*sec)
Degradation : % after
Deg. product :
Method : other (measured): Based on OPPTS: 835.5270, OECD Draft "Phototransformation of Chemicals in Water - Direct and Indirect Photolysis", August, 2000.
Year : 2001
GLP : no
Test substance :

Method : Test matrices:
1.) Direct photolysis: Water
Indirect: 2.)H2O2/water (1:1 molar equivalent); 3.) Soil/dilute aqueous CaCl2 solution (0.7 g/5mL) (3 soil types - loam, clay loam, sandy clay loam); 4.)Soil/dilute aqueous CaCl2 solution with H2O2; 5.) Fe2O3/water (Fe3+ at 24X molar excess); 6.) Fe2O3/water with H2O2; 7.) Commercial (Aldrich) humic material prepared as in OPPTS 835.5270; + unexposed controls (kept in the dark)

Duration: 69.5 to 72 hours

Samples were analyzed by quantitative LC/MS and GC/MS techniques

Result : Direct Photolysis: rate of photodegradation is negligible.

Indirect Photolysis: Degradation of N-EtFOSE alcohol was observed in each matrix. Primary degradation products: PFOA, N-EtFOSA, and FOSA; under certain conditions, trace levels (near the quantitation limits) of other potential degradation products (heptadecafluorooctanes and PFOS) were

also observed. Unclear whether these compounds were produced by the degradation of N-EtFOSE alcohol; also possible: degradation products of low-level impurities in the original sample material.

Iron oxide/H2O2, half-life of N-EtFOSE alcohol: about 40 days under these conditions.

General problem: purity of N-EtFOSE alcohol 97.8%, 2.2% unknown.

Test substance : 2-N-Ethyl perfluorobutanesulfonamidoethanol (NMeFBSE alcohol)
Reliability : (2) valid with restrictions
22.12.2006 (59)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method : other (measured)
Year : 2000
GLP : no
Test substance :

Method : The 3M White Paper, March 1, 2000, section 9.2, p.37, states "The preliminary results suggest that PFOS is unchanged as a result of light exposure".
Result : EtFOSE alcohol, MeFOSE alcohol, EtFOSA and MeFOSA as well as a surfactant and foamer product all appeared to undergo photolysis to FOSA, PFOA a hydride, and olefins. PFOS was not detected. One product, an aromatic perfluorooctane sulfonate, did photodegrade to form PFOS.
Test substance : EtFOSE alcohol, MeFOSE alcohol, EtFOSA and MeFOSA
29.12.2006 (62)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : EPA OPPTS 835.2110
Year : 2001
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : This method is based on OPPTS:835.2110 and has been modified to give additional information. Specifically, multiple time points over far longer periods of time are used to provide additional information regarding the hydrolytic behavior. Additional pH's are tested to provide insight into acid/base catalysis.
Result : A study was performed of the aqueous hydrolysis of APFO at 50°C and extrapolated the results to 25°C. Six different pH levels were used, though data from 2 of these pH levels (3.0 and 11) failed to meet the data quality objectives. Also rejected was the data for pH = 1.5. Data for the remaining pH levels (5.0, 7.0, and 9.0) indicate no clear dependence of the degradation rate of APFO on pH. From the data pooled over these three pH levels, the hydrolytic half-life of APFO at 25°C is greater than 92 years, with the most likely value of 235 years. From the mean value and precision of APFO concentrations, the hydrolytic half-life is estimated to be greater than 97 years.
Reliability : (1) valid without restriction

Comparable to guideline study

13.01.2006 (53)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement : other: environmental concentration and concentration at contaminated site
Media : air
Concentration :
Method : other

Method : Air samples were collected during a ten week period from November 2003-January 2004 along the fenceline of the DuPont Washington Works plant in West Virginia.
Remark : The reporting limit was between 120 and 170 ng/m3.
Result : OVS tube monitoring during the ten weeks measured PFOA levels from <120 ng/m3 to 900 ng/m3.
Test substance : PFOA
Reliability : (2) valid with restrictions

03.01.2007 (81)

Type of measurement : background concentration
Media : air
Concentration :
Method : other

Method : Air samples were collected in the town of Oyamazaki (Kyoto Pref., Japan) and Morioka City (Iwate Pref., Japan) and evaluated for concentration of air-borne PFOA and PFOS. These 2 cities were selected because serum levels of PFOA suggest that the former is representative of highly contaminated areas, while the latter of low contaminated areas.
Remark : The reporting limit (RL) was 0.46 pg/m3 at Morioka and 0.33 pg/m3 at Oyamasaki.
Result : The lowest limits of detection (LOD)of PFOA and PFOS were determined to be 0.138 ng for PFOA and 0.091 ng for PFOS in the samples and the LOQ of PFOA and PFOS were 0.460 and 0.302 ng, respectively. The PFOA and PFOS concentrations of all the samples were larger than the quantification limit. To quantify the PFOA and PFOS concentration in the air, the background levels were subtracted from the sample values. The annual geometric means of the PFOA and PFOS concentrations in the air were 262.8 and 5.2 pg/m3 for the town of Oyamazaki and 2.0 and 0.7 pg/m3 for Morioka City. It was significantly higher in Oyamazaki than in Morioka City for both PFOA and PFOS. There were no significant difference of PFOS concentrations in Morioka City and Fukuchiyama, where PFOS concentrations are assumed to be typical of rural areas (0.6 pg/m3).
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (308)

Type of measurement : other: environmental concentration
Media : air
Concentration :
Method : other

Method : The concentrations of PFOA and PFOS were determined in vacuum

cleaner dust collected in Japanese homes.

Remark : The reporting limit (RL) was 50 ng/g.

Result : PFOA and PFOS were detected in all the dust samples collected from vacuum cleaners in Japanese homes. The ranges were 69-3700 ng/g for PFOA and 11-2500 ng/g for PFOS.

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (449)

Type of measurement : background concentration
Media : air
Concentration :
Method : other

Method : A series of perfluorinated compounds (PFCs) including perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been recently measured in a variety of environmental samples and biological matrices. In order to better understand the human exposure routes of these chemicals, levels of PFOS, PFOA, perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHS) and perfluorooctane sulfonamide (PFOSA) in house dust samples were investigated.

Result : The data revealed a correlation between the concentrations of PFCs and the percentage of carpeting in the house; older houses tended to have less carpeting, hence lower levels of these perfluorinated compounds in their dust.

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

13.01.2006 (388)

Type of measurement : other: Environmental Concentration
Media : air
Concentration :
Method : other

Method : Air samples were collected with OSHA Versatile Sampling (OVS) method tubes and High-Volume Sampling (HVS) equipment within a two mile radius of the Washington Works, DuPont site in West Virginia from August-October, 2005.

Remark : The reporting limit (RL) was 0.09 ng/tube.

Result : The OVS samples ranged from limit of detection (0.09-0.64 ng/tube fraction) to 60.2 ng/m3 of PFOA. HVS samplers measured PFOA in the range of 0.01 to 75.9 ng/m3.

Test substance : PFOA

Reliability : (2) valid with restrictions

03.01.2007 (240)

Type of measurement : concentration at contaminated site
Media : soil
Concentration :
Method : other

Method : Soil was collected in two borings up to 56-feet deep near a manufacturing site in West Virginia.

Remark : The reporting limit (RL) was 0.17-0.19 ng/g ww.

Result : The results ranged from below the reporting limit (0.17 ng/g) to 170 ng/g dry weight.

Test substance : APFO

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (226)

Type of measurement : concentration at contaminated site
Media : soil
Concentration :
Method : other

Method : Soil was collected in 2003 from zero to one feet deep near a manufacturing site in West Virginia.
Remark : The reporting limit (RL) was 2.1-21 ng/g dw.
Result : The results ranged from 2.2 to 700 ng/g dry weight.
Test substance : Not specified
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (238)

Type of measurement : concentration at contaminated site
Media : soil
Concentration :
Method : other

Method : Soil was collected two months after fire fighting foam that contained perfluorinated compounds had been used to put out a refinery fire in Japan.
Remark : Year of sampling = 2003
The reporting limit (RL) = No information
Result : The mean concentration for PFOA was 2870 pg/g (dry weight basis). Due to the impacts of manufacturing and fire fighting at these locations, the results cannot be considered typical environmental levels in soil.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (638)

Type of measurement : other: Environmental Concentration
Media : soil
Concentration :
Method : other

Method : Soil samples were collected on-site at the DuPont Washington Works West Virginia site from soil 3"-6" and 6"-12" below the surface.
Remark : The reporting limit (RL) = No information
Result : The soil samples collected from the 3"-6" intervals ranged from 72-130 ppb PFOA. Those soil samples in the 6"-12" interval contained PFOA in the range of 44-130 ppb PFOA.
Test substance : PFOA
Reliability : (2) valid with restrictions

03.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : soil
Concentration :
Method : other

Method : Soil samples were collected from the sludge application area of the 3M Decatur, AL facility during February and March, 2006. Samples were collected at 0"-3", 3"-6", 6"- 12", several 0.5 foot intervals between one and ten feet and several five foot intervals between ten feet and either the uppermost water level called the residuum or the lower bedrock limestone. Background soil samples were also collected at the same intervals and new soil borings were drilled in areas where older ground water wells,

designated as the Letter of Intent (LOI) wells occur.

Remark : The reporting limit (RL) = 0.2 ng/g (ppb)

Result : The range of PFOA concentrations for the soil boring intervals in the sludge application fields is as follows: 29-3140 ppb for 0"-3"; 34.2-5690 ppb for 3"-6"; 18.5-1870 ppb for 6"-12"; 25.3-8780 ppb for 1'-10'; and 14.1-3800 ppb for over 10'. Background PFOA levels in the sludge application control and in the non-sludge application background area were both well below the sludge application levels and ranged between 0.2 (non-detect) and 9.92 ppb. The soil samples collected from the borings in the LOI areas were significantly lower than the sludge application area soils also but higher than background with a range of PFOA levels between 0.2 (non-detect) and 810 ppb.

Test substance : PFOA

Reliability : (2) valid with restrictions

03.01.2007 (57)

Type of measurement : concentration at contaminated site

Media : soil

Concentration :

Method : other

Method : Soil samples were collected from a contaminated site in The Netherlands (2004-2005).

Remark : Reporting limit was 0.4 ng/g dw

Result : PFOA concentration was 8.3 ng/g dw

Source : Data was taken from SIAR Table 19 (December 12, 2006).

Test substance : PFOA

05.01.2007 (149)

Type of measurement : concentration at contaminated site

Media : ground water

Concentration :

Method : other

Method : PFOA was determined in ground water samples taken near two manufacturing sites in the USA [Cottage Grove, MN and Decatur, AL].

Remark : Year of sampling = 2001-2003
The reporting limit (RL) = No information

Result : At two manufacturing sites in the USA [Cottage Grove, MN and Decatur, AL], the levels of PFOA in ground water ranged from not detected to 3,400,000 ng/L.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (539)

Type of measurement : concentration at contaminated site

Media : ground water

Concentration :

Method : other

Method : PFOA was determined in ground water potentially impacted by previous fire-fighting activities.

Result : In ground water potentially impacted by previous fire-fighting activities in the USA, the measurements ranged from below the reporting limit (which decreased from 36,000 ng/L in 1999 to 3000 ng/L in 2003) to 6,570,000 ng/L. Five years after the fire-fighting activity, levels of PFOA in the ground water ranged from below the level of detection (3000 ng/L) to 105,000 ng/L.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with

acceptable restrictions

03.01.2007 (443) (444)

Type of measurement : concentration at contaminated site
Media : ground water
Concentration :
Method : other

Method : PFOA was determined in ground water samples taken at two manufacturing sites.
Remark : Year of sampling = 2001-2003
The reporting limit (RL) = 10 ng/l
Result : At two manufacturing sites, PFOA was found in the ground water at levels up to 47,000 and 51,000 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

05.01.2007 (216) (226)

Type of measurement : concentration at contaminated site
Media : ground water
Concentration :
Method : other

Method : A survey was conducted of groundwater wells in Ohio within a 2-mile radius of a Parkersburg, WV manufacturing plant. Samples were analyzed for C-8 concentrations.
Remark : The reporting limit (RL) = 10-50 ng/l
Result : C-8 was found in 48 of the 62 sampled wells at levels ranging from less than the level of detection (50 ng/L) up to 8700 ng/L.
Test substance : APFO
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (215)

Type of measurement : concentration at contaminated site
Media : ground water
Concentration :
Method : other

Method : Groundwater samples from six monitoring wells in the Chamber Works site in Deepwater NJ were tested for PFOA from May 2003 to June 2003.
Remark : The reporting limit (RL) = 0.050 µg/L
Result : The concentrations ranged from 191 to 5230 ng/L. All of the samples tested were positive and the Limit of Quantification (LOQ) was 0.050 µg/L. All the samples tested in May 2003 were positive and five interceptor wells contained PFOA and concentrations ranged from 354 to 46,800 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions

05.01.2007 (236)

Type of measurement : other: Environmental Concentration
Media : ground water
Concentration :
Method : other

Method : Groundwater monitoring wells located at three different landfill sites in the vicinity of the Washington Works plant were monitored for PFOA and APFO between 1996 and 2006. The landfills are the Dry Run landfill, the Local landfill and the Letart landfill.

Remark : The reporting limit (RL) = 50 ng/l (APFO)
Result : PFOA and APFO levels at the Local landfill ranged from 0.141-69 ug/l and <0.050-91.1 ug/l, respectively. For the Dry Run landfill, PFOA and APFO ranged from <0.050-32.6 ug/l and <0.050-39.0 ug/l, respectively. PFOA and APFO levels at the Letart landfill were measured at a range between 0.126-20,200 ug/l and 0.058-57,200 ug/l, respectively.
Test substance : APFO and PFOA
Reliability : (2) valid with restrictions
03.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : ground water
Concentration :
Method : other

Method : Groundwater has been monitored at the Washington Works facility in West Virginia from 1996-2006 at groundwater monitoring well locations on the plant site. APFO levels have been measured since 1996 and PFOA levels have been measured since 2004.
Remark : The repor`ting limit (RL) = No information
Result : APFO levels at 70 different groundwater wells at the plant between 1996 and 2006 ranged from <0.050 to 466,000 ug/l. PFOA levels in groundwater at Washington Works between 2004 and 2006 ranged from 537-118,000 ng/l.
Test substance : APFO and PFOA
Reliability : (2) valid with restrictions
04.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : ground water
Concentration :
Method : other

Method : Groundwater concentrations of PFOA were measured in the sludge application area, the sludge application control and the LOI area wells at the 3M Decatur, AL facility after completion of the soil sampling in February and March, 2006. Wells in the sludge application area were completed at differing levels in the aquifer, either the upper residuum or the lower limestone bedrock layer.
Remark : The reporting limit (RL) = 25 ng/l
Result : The wells in the sludge application area contained PFOA in the range between 2.27 to 3857 ug/l. The control sludge application well water contained lower PFOA levels in the range between 0.220 - 94.7 ug/l. The LOI PFOA levels ranged from 0.025 (non-detect) to 1333 ug/l.
Test substance : PFOA
Reliability : (2) valid with restrictions
03.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : ground water
Concentration :
Method : other

Method : Results are provided of an investigation on the discovery of 12 perfluorinated surfactants (PS) in different surface and drinking waters. Surface and drinking water samples were collected from different sampling sites: Surface waters: samples taken from the rivers Rhine, Ruhr, Moehne and some of their tributaries. Further samples were taken from the Rhine-Herne-Canal and the Wesel-Datteln-Canal. Drinking waters: samples taken in public buildings of the Rhine-Ruhr area. After sample clean-up and concentration by solid-phase extraction, the perfluorinated surfactants were determined using HPLC-MS/MS.

Remark : The reporting limit was 2 ng/l
Result : All measured concentrations (sum of seven mainly detected components) in the Rhine river and its main tributaries (mouths) were determined below 100 ng/L. The Ruhr river (tributary of the Rhine) showed the highest concentration (94 ng/L), but with a completely different pattern of components (PFOA as major component), as compared with the other tributaries and the Rhine river. Further investigations along the Ruhr river showed remarkably high concentrations of PS in the upper reaches of the Ruhr river and the Moehne river (tributary of the Ruhr) (Ruhr: up to 446 ng/L, Moehne: up to 4385 ng/L). The maximum concentration of all drinking water samples taken in the Rhine-Ruhr area was determined at 598 ng/L with the major component PFOA (519 ng/L).
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (558)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : ground water
Concentration :
Method : other

Method : 2003/2004; Ground water samples collected at Washington Co. landfill, USA.
Remark : Reporting limit (RL) = No information
Result : 1300-70,000 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (441)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : ground water
Concentration :
Method : other

Method : 2003/2004; Ground water from private wells in the vicinity of the Washington Co. landfill, USA.
Remark : Reporting limit (RL) = No information
Result : < 1000 ng/L (PFOA detected but not quantified).
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (441)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : other

Method : PFOA was determined in samples from a creek after a spill of fire retardant foam.
Remark : Year of sampling = 2000-2001
Reporting limit (RL) = 9 ng/l
Result : The highest measurement from a creek after a spill of fire retardant foam was 11,000 ng/L, while the maximum upstream concentration was 33 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
03.01.2007 (445)

Type of measurement : other: environmental concentration and concentration at contaminated site
Media : surface water

Concentration :
Method : other

Method : PFOA was determined downstream from a manufacturing facility [Tennessee River, Decatur, AL].
Remark : Reporting limit (RL) = 25 ng/l
Result : Downstream from a manufacturing facility [Tennessee River, Decatur, AL], the highest reported concentration was 598 ng/L, while upstream results were less than the reporting limit of 25 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (303)

Type of measurement : background concentration
Media : surface water
Concentration :
Method : other

Method : PFOA was determined in areas away from spills and from manufacturing sites.
Remark : Reporting limit (RL) = 25 ng/l
Result : Away from spills and manufacturing sites, the highest reported concentration of PFOA in surface water was 760 ng/L, which was from Port St. Lucie, Florida.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : PFOA was determined in rain water from a sample collected in Delaware, USA. Other samples were taken from rain water collected in Canada, New York, and Maryland and in fresh water taken from the Great Lakes and its tributaries.
Remark : Reporting limit (RL) = 0.5 to 10 ng/L
Result : In rain water, PFOA has been detected up to 90 ng/L in a sample from Delaware, USA. Other samples taken from rain water collected in Canada, New York, and Maryland contained up to 4 ng/L of PFOA. In fresh water taken from the Great Lakes and its tributaries, PFOA levels ranged from less than the reporting limit of 0.5 ng/L to 10 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (547)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : PFOA was determined in samples taken from the Great Lakes.
Remark : Reporting limit (RL) = 13 ng/L
Result : In samples taken from the Great Lakes, levels of PFOA ranged from 21 to 47 ng/L in Lake Erie and from 15 to 70 ng/L from Lake Ontario.
Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (104)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : other

Method : PFOA was quantified in river water near a wastewater treatment plant.
Remark : Year of sampling = 2004
Reporting limit (RL) < 2 ng/L
Result : PFOA was quantified in river water at 8.7 ng/l.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (105)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : PFOA was analyzed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.06 ng/l
Result : In samples collected from Nordic rain water and from Nordic lakes, PFOA ranged from 8.2 to 17 ng/L (rain water) and 4.8 to 8.2 ng/L (lake water).
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : PFOA was determined in samples collected in Germany.
Remark : Reporting limit (RL) = 1 ng/l
Result : PFOA levels ranged up to 8 ng/L.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (403)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : PFOA and PFOS concentrations were analyzed in surface water samples collected from all over Japan. Water samples were collected from rivers, coastal sea waters and tap waters. For all sampling, a two-L sample was collected. Samples were passed through the Presep-C Agri column at a flow rate of 10 mL/min using a Waters Concentrator System (Concentrator Plus, Waters, Tokyo, Japan). Presep-C cartridges were then eluted with 1.5 mL of methanol and concentrated at room temperature. The methanol extracts were chromatographed using HPLC and Mass spectra were taken

on an LC/MS. The fragment ions for PFOA m/z 413 (C7F15CO2-) and for PFOS m/z 499 (C8F17SO3-) were monitored for quantification. The lowest limits of detection (LOD) (ng/L) were 0.06 for PFOA and 0.04 for PFOS. The lowest limits of quantification (LOQ) (ng/L) were 0.1 for both analytes.

Remark : Reporting limit (RL) = 0.1 ng/l

Result : The levels [geometric mean (GM); geometric standard deviation (GS)] (ng/L) of PFOA and PFOS in the surface waters were GM (GS): 0.97 (3.06) and 1.19 (2.44) for Hokkaido-Tohoku (n=16); 2.84 (3.56) and 3.69 (3.93) for Kanto (n=14); 2.50 (2.23) and 1.07 (2.36) for Chubu (n=17); 21.5 (2.28) and 5.73 (3.61) for Kinki (n=8); 1.51 (2.28) and 1.00 (3.42) for Chugoku (n=9); 1.93 (2.40) and 0.89 (3.09) for Kyushu-Shikoku (n=15). The GM of PFOA in Kinki was significantly higher than in other areas. Systematic searches of Yodo and Kanzaki Rivers revealed two potential sources, a public-water-disposal site for PFOA and an airport for PFOS. The former was estimated to release 18 kg of PFOA/day. PFOA in drinking water in Osaka city [40 (1.07) ng/L] was significantly higher than in other areas. The present study confirms that a large amount of PFOA is produced and released in Kink, and causes drinking water contamination.

Source : Data was taken from SIAR Table 19 (December 12, 2006).

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

05.01.2007 (535) (536)

Type of measurement : other: environmental concentration

Media : surface water

Concentration :

Method : other

Method : PFOA was detected in Michigan water samples.

Remark : Year of sampling = 2001-2003
Reporting limit (RL) = 8 ng/l

Result : The maximum concentration measured was 36 ng/L. Background concentrations were found to be less than 8 up to 16 ng/L for PFOA. The highest concentrations were detected in the waters of southwestern Michigan. Elevated concentrations of PFOA were detected in and around Flint, MI and in Saginaw Bay, MI waters.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (556)

Type of measurement : concentration at contaminated site

Media : surface water

Concentration :

Method : other

Method : PFOA was measured in fresh water samples one month after fire fighting foam was used to fight a refinery fire.

Remark : Year of sampling = 2003
Reporting limit (RL) = No information

Result : The mean PFOA concentration found in runoff into Tomakomai Bay was 160 ng/L. Two months after the fire, snow near Tomakomai contained 18 ng/L of PFOA.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (638)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : other

Method : PFOA concentrations were determined in samples taken at a manufacturing site.
Remark : Reporting limit (RL) = No information
Result : In samples taken at a manufacturing site, the maximum level found in fresh river water was 89 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (217)

Type of measurement : other: environmental concentration
Media : surface water
Concentration :
Method : other

Method : The aim of the study was to assess the levels and distribution of perfluorinated alkylated substances (PFAS) in the Nordic environment and to trace differences in contaminant concentrations and patterns between different countries and types of matrices.
Remark : Reporting limit (RL) = No information
Result : Median levels for PFOA were 5.2 ng/L in seawater, 7.8 ng/L in lake water, 13.1 ng/L in rainwater, 20.5 ng/L in sewage effluent and 297 ng/L in landfill effluent.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (88)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : other

Method : Samples of surface water from the Delaware river were collected and tested for PFOA in June 2003 from 30 locations.
Remark : Reporting limit (RL) = 10 ng/l
Result : The concentrations of PFOA in the surface water samples ranged from not quantifiable to 577 ng/L, with a Limit of Detection (LOD) of 10 ng/L and a Limit of Quantification of 50 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions

05.01.2007 (236)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : Surface water samples (12) were collected in the Tennessee River and a nearby creek called Baker's Creek adjacent to the 3M Decatur, AL facility in April, 2006. Each sample was analyzed twice for PFOA. Other surface water samples (16) were taken in a longitudinal direction along the length of the river along with a set of 30 samples collected across the river.
Remark : Reporting limit (RL) = 4.92 ng/l (longitudial study) but no information was available for the samples taken adjacent to the facility.

Result : The range of averaged concentrations of PFOA for the 12 samples is 73.4 to 420 ng/ml (ppb). The range of PFOA concentrations for the longitudinal samples (16) is 4.92 (non-detect)-26 ng/ml. The range of PFOA concentrations for the transect samples (30) is 2.66-435 ng/ml.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : Surface water samples (12) were collected in the Tennessee River adjacent to the 3M Decatur, AL facility in April, 2006. Each sample was analyzed twice for PFOA.
Remark : Reporting limit (RL) = No information was available for the samples taken adjacent to the facility.
Result : The range of averaged concentrations of PFOA for the 12 samples is 0.0977 to 70.4 ng/ml (ppb).
Test substance : PFOA
04.01.2007 (57)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : other

Method : Freshwater samples were taken from a canal after receiving wastewater from a fire incident where fire fighting foam has been used in The Netherlands (2004-2005).
Remark : Reporting limit was 80 ng/L
Result : PFOA concentration was 160 ng/L
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (149)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : Water samples from Tour-Chyan river, Taiwan.
Remark : Reporting limit (RL) = 0.8 ng/l
Result : 113 ng/l (mean)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : 2005; Surface water sampled within the 3M Guin (USA) facility at two locations.
Remark : Reporting limit (RL) = Ca. 25 ng/l
Result : Location #1 = < 25-10,800 ng/L
Location #2 = < 25-9100 ng/L
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (2)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : 2004; Water samples collected from the Great Lakes (11 locations).
Remark : Reporting limit (RL) = 1-4 ng/l
Result : 2-7 ng/l
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (270) (271)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : River water samples collected in the Kyoto area; Japan.
Remark : Reporting limit (RL) = 7.9 ng/l
Result : 7.9-110 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (399)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : 2004; Water samples were collected from streams of the Shihwa industrial zone and Lake Shihwa, South Korea.
Remark : Reporting limit (RL) = 0.9 ng/l
Result : 0.9-62 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (530)

Type of measurement : other: Environmental Concentration
Media : surface water
Concentration :
Method : other

Method : Surface water samples collected in the mid-western US (Minneapolis, remote areas of Minnesota, shore of Lake Superior, and Voyageurs National Park along the US-Canadian border).
Remark : Reporting limit (RL) = 0.29-0.58 ng/l
Result : 0.14-0.66 ng/L (remote lakes)
0.45-19 ng/L (urban surface waters)
0.28-3.4 ng/L (Lake Michigan)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (552)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA concentrations were determined in samples taken from the Atlantic Ocean at depths to 5300 meters.
Remark : Reporting limit (RL) = No information

Result : In samples taken from the Atlantic Ocean at depths to 5300 meters, PFOA concentrations ranged from 0.050 to 0.10 ng/L throughout the surface waters of the North and South Atlantic Ocean.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (546)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA concentrations were determined in samples taken from the North Sea, at the mouth of the river Elbe, along the Elbe plume towards the north, and in the southern German Bight. In August 2003 the investigation was extended into the whole North Sea.
Remark : Year of sampling = 2003
Reporting limit (RL) = 0.5 ng/l
Result : In samples taken from the North Sea, PFOA concentrations ranged from the reporting limit (0.5 ng/L) to 20 ng/L. The highest concentrations were observed for PFOA and perfluorooctanesulfonate (PFOS) at the mouth of the river Elbe. Along the Elbe plume towards the north, concentrations of the major compounds decrease to 3 to 6 ng/L, while to the open sea they drop to 0.5 to 1.2 ng/L. In the southern German Bight, a different pattern with higher PFOA but low PFOS was observed, indicating a different source. In August 2003 the investigation was extended into the whole North Sea. At most stations of the open sea only PFOA could be detected at concentrations of ca. 0.5 ng/L, all other target compounds were below the present detection limits.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (117)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA was analyzed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.06 ng/l
Result : In 15 sea water samples collected in the North Atlantic near Iceland, in the North Sea near Denmark and the Faroe Islands, and in the Baltic Sea near Finland, PFOA concentrations ranged from 3.5 to 8.5 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : concentration at contaminated site
Media : other: Salt water
Concentration :
Method : other

Method : PFOA was measured in water taken from Tomakomai Bay in Japan one month after fire fighting foam was used to fight a refinery fire.
Remark : Year of sampling = 2003
Reporting limit (RL) = No information

Result : The mean PFOA concentration was 4.15 ng/L. One month later, the mean concentration had fallen to 2.67 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (638)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA was measured in water taken from several sites including Tokyo Bay, the coastal waters of Hong Kong, South China, and Korea, the mid-Atlantic Ocean, the Sulu Sea, the South China Sea, and the eastern, and central to western Pacific Ocean.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = approx. 0.01 ng/l
Result : PFOA concentrations ranged as follows: Tokyo Bay (154-192 ng/L); mid-Atlantic Ocean (0.10-0.15 ng/L); Sulu Sea (0.076-0.51 ng/L); South China Sea (0.16-0.42 ng/L); western Pacific Ocean (0.136-0.142 ng/L); central to eastern Pacific Ocean (0.015-0.056 ng/L).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (639)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA was measured in the coastal waters of Hong Kong, South China, and Korea.
Remark : Year of sampling = 2003
Reporting limit (RL) = 0.02 ng/l
Result : PFOA concentrations ranged from 0.24 to 320 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (566)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : PFOA was measured in several coastal Pacific ocean locations near Japan including the Sea of Kushiro, Mutsu Bay, Honjo Marina, Funabashi Coast, and the Koshien Coast.
Remark : Reporting limit (RL) = 0.1 ng/l
Result : PFOA concentrations ranged from 1.9 to 450 ng/L.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

05.01.2007 (535)

Type of measurement : other: environmental concentration
Media : other: Salt water
Concentration :
Method : other

Method : A reliable and highly sensitive analytical method was developed by which to monitor perfluorinated compounds in oceanic waters. The method developed is capable of detecting PFOS, perfluorohexanesulfonate (PFHS), perfluorobutanesulfonate (PFBS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), and perfluorooctanesulfonamide (PFOSA) at a few pg/L in oceanic waters. The method was applied to seawater samples collected during several international research cruises undertaken during 2002-2004 in the central to eastern Pacific Ocean (19 locations), South China Sea and Sulu Seas (5 locations), north and mid Atlantic Ocean (12 locations), and the Labrador Sea (20 locations). An additional 50 samples of coastal seawater from several Asian countries (Japan, China, Korea) were analyzed.
Remark : Year of sampling = 2002-2004
Reporting limit (RL) = approx. 0.01 ng/l
Result : PFOA was found at levels ranging from several thousands of pg/L in water samples collected from coastal areas in Japan to a few tens of pg/L in the central Pacific Ocean. PFOA was the major contaminant detected in oceanic waters, followed by PFOS.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

05.01.2007 (640)

Type of measurement : other: Environmental Concentration
Media : other: salt water
Concentration :
Method : other

Method : Coastal waters collected from Jun-Wen estuary and Chi-Ku lagoon, Taiwan.
Remark : Reporting limit (RL) = 0.8 ng/l
Result : 130-270 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA

05.01.2007 (602)

Type of measurement : other: Environmental Concentration
Media : other: salt water
Concentration :
Method : other

Method : 2004; Elbe river estuary and German Bight.
Remark : Reporting limit (RL) = 0.013 ng/l
Result : 0.140-6.82 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA

05.01.2007 (594)

Type of measurement : other: Environmental Concentration
Media : other: salt water
Concentration :
Method : other

Method : 2004; North Altlantic, North Polar Sea
Remark : Reporting limit (RL) = 0.008 ng/l

Result : 0.035-0.097 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (594)

Type of measurement : other: Environmental Concentration
Media : other: salt water
Concentration :
Method : other

Method : Water samples collected from the Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 0.8-10 ng/l
Result : 50 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: salt water
Concentration :
Method : other

Method : Water samples were collected in the coastal areas of China and Korea and in the mid Atlantic Ocean and in the Sulu Sea.
Remark : Reporting limit (RL) = approx. 0.01 ng/l
Result : Coastal area of China = 0.243-15.300 ng/L
Coastal area of Korea = 0.239-11.300 ng/L
Coastal area of Hong Kong = 0.673-5.450 ng/L

Offshore of Japan = 0.137-1.060 ng/L

Mid Atlantic Ocean = 0.100-0.439 ng/L
North Atlantic Ocean = 0.160-0.338 ng/L
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (590) (640)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: salt water
Concentration :
Method : other

Method : 2003; 3 months after fire fighting foam was used; Tomakomai Bay (Japan).
Remark : Reporting limit (RL) = Ca. 3 ng/l
Result : 62.4-63.7 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (589)

Type of measurement : concentration at contaminated site
Media : drinking water
Concentration :
Method : other

Method : Concentrations of PFOA were measured and evaluated in water samples from the Oakdale municipal well.
Remark : Reporting limit (RL) = 25 ng/l
Result : The well sample concentrations ranged from not detected (ND) to 858 ng/L in December 2004. Out of nine samples, there was one sample below the detection limit of 25 ng/L. In August 2005, the well concentrations ranged from 288 to 856 ng/L; of the four samples, there were no samples below the detection limit of 25 ng/L.

Test substance : PFOA
Reliability : (4) not assignable
04.01.2007 (93)

Type of measurement : other: Environmental Concentration
Media : drinking water
Concentration :
Method : other

Method : DuPont has been sampling public water supply systems in West Virginia and Ohio for APFO since 2002 and for APFO and PFOA since 2004. Twelve systems are sampled in West Virginia and seven systems are sampled in Ohio each year for APFO and PFOA. Additionally, DuPont has sampled twenty-five residential water wells in the vicinity of Washington Works on a quarterly basis for APFO since 2002 and for APFO and PFOA since 2004.
Remark : Reporting limit (RL) = 1 ng/l
Result : The PFOA concentrations in the public supply systems have ranged from a low of 1 ng/l (non-detect) to 71,900 ng/l. The residential well samples have ranged from a low of 5 ng/l (non-quantifiable) to 27,100 ng/l.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : other: freshwater
Concentration :
Method : other

Method : 2004; Water samples collected from nine major water bodies of New York State, USA.
Remark : Reporting limit (RL) = 2.5 ng/l
Result : 10-173 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (555)

Type of measurement : other: Environmental Concentration
Media : other: rainwater
Concentration :
Method : other

Method : Precipitation samples were collected at the DuPont Washington Works site, West Virginia between August 25-26, 2005 at the same locations where ambient air samples were collected.
Remark : Reporting limit (RL) = 8.8 ng/l
Result : Precipitation samples had PFOA levels that ranged from < 8.8 ng/l to 1660 ng/l. Out of eleven samples, seven were non-quantifiable, four ranged between 10.2 ng/l and 52.9 ng/l and one measured 1660 ng/l.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : other: rain water
Concentration :
Method : other

Method : 2004; Rain water samples collected in Winnipeg; Canada.
Remark : Reporting limit (RL) = 7.2 ng/l
Result : < 7.2 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).

Test substance : PFOA
05.01.2007 (421)

Type of measurement : other
Media : food
Concentration :
Method : other

Method : A market basket sampling was taken of PFOA residue in a total of over 200 samples taken from green beans, apples, pork muscle, cow milk, chicken muscle, chicken eggs, bread, hot dogs, catfish, and ground beef.
Result : Measurable quantities of PFOA, ranging up to 2.35 ng/g, were found in two ground beef samples, two bread samples, two apple samples, and one green bean sample.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment
03.01.2007 (11)

Type of measurement : other: Environmental Concentration
Media : food
Concentration :
Method : other

Method : Researchers at the University of Pennsylvania conducted questionnaire and serum PFOA measurements in a stratified random sample on volunteers residing in locations with the same residential water supply but with higher and lower potential air PFOA exposure in West Virginia and Ohio.
Result : Occupational exposure from production processes involving PFOA had additive effects; no other occupations contributed. Serum PFOA levels depended on the source of residential drinking water, and not potential air exposure. For public water users, the best-fit model included age, tap water drinks per day, servings of home grown fruit and vegetables, and carbon filter use. There was a statistically significant increase in the mean serum PFOA associated with increasing numbers of weekly servings of fruits and vegetables from a local garden. Additionally, there was an increase in serum PFOA with servings of meat or game grown or harvested locally.
Test substance : PFOA
Reliability : (2) valid with restrictions
03.01.2007 (250)

Type of measurement : other
Media : other: food and consumer products
Concentration :
Method : other

Method : PTFE cookware was analyzed for its PFOA content before and after heating to 320°C (3 pans). Simulated food cooking using PTFE sealant film as a surrogate for PTFE cookware was also analyzed for PFOA.

Microwave popcorn bags with a fluorotelomer coating were analyzed for PFOA and fluorotelomers (chemical species not specified). Popcorn oil was tested for the presence of fluorotelomer and PFOA before and after heating the bag to over 200°C).
Result : PTFE coating: contains 4-75 µg/kg PTFE before heating, no APFO could be determined after heating the empty pan. Simulated food cooking using PTFE sealant (this represents a conservative approach to estimating migration from PTFE) showed a migration of 17% of the PFOA contained in PTFE migrating into oil at 175°C. Results suggest that significant amounts of PFOA are not generated and remain in the cookware after an extreme heating event.

Perfluoro paper additives/coatings: before heating 1.4 mg/kg fluorotelomer (chemical species not specified) in popcorn oil; after heating additional 2.1 mg/kg fluorotelomer in popcorn oil.

PFOA is present in microwave popcorn bag paper at amounts equal to or less than 300 ug/kg. After microwaving Miglyol in popcorn bags <1 µg/kg PFOA in Miglycol was detected. Subsequent analyses of these bags suggests these particular test bags had the fluorotelomer coating/additive containing PFOA primarily on the outside of the bags.

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (82)

Type of measurement : other: other: environmental concentration and concentration at contaminated site
Media : sediment
Concentration :
Method : other

Method : PFOA was measured near manufacturing sites in the USA (Decatur, AL; Mobile, AL; Columbus, GA; Pensacola, FL) and for cities with no manufacturing sites (Port St. Lucie, FL and Cleveland, TN).
Remark : Year of sampling = 1999-2000
Reporting limit (RL) = 0.2 ng/g ww
Result : Near manufacturing sites in the USA (Decatur, AL; Mobile, AL; Columbus, GA; Pensacola, FL), the results were below the reporting limit of 0.2 ng/g wet weight, whereas results for cities with no manufacturing sites (Port St. Lucie, FL and Cleveland, TN) ranged from below the reporting limit to 1.8 ng/g dry weight. A year later, sediment from the city (Port St. Lucie, FL) reporting 1.8 ng/g dry weight was re-sampled, and the results were below the reporting limit.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : other: Sediment and Suspended Matter
Concentration :
Method : other

Method : Perfluorinated compounds were measured in the Dutch aquatic environment.
Remark : Year of sampling = 2004
Reporting limit (RL) = 0.4 ng/g dw
Result : According the information provided by De Voogt (2004), PFOA was detected in 11 out of 33 sediment and suspended matter samples. The single highest result was 24 ng/g dry weight in a sample collected in the Netherlands. Other results from this study were below the reporting limit (0.4 ng/g dry weight).
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (148) (542)

Type of measurement : other: environmental concentration
Media : sediment
Concentration :
Method : other

Method : PFOA was analyzed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.20 ng/g ww
Result : Only 2 of the 13 samples analyzed from Nordic countries had levels above the limit of quantification (0.20 ng/g wet weight). The values were 0.28 and 0.31 ng/g wet weight.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : other: environmental concentration
Media : sediment
Concentration :
Method : other

Method : Sediments were collected from the San Francisco bay area, Palo Alto mud flats, Hayward, CA, Baltimore, MD, and Corvallis, OR and PFOA concentrations were determined.
Remark : Reporting limit (RL) = 0.011 ng/g dw
Result : The concentration of PFOA in sediments ranged from the limit of detection to 0.625 ng/g (dry weight).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (318)

Type of measurement : other: Environmental Concentration
Media : sediment
Concentration :
Method : other

Method : Sediment samples (12) were collected in the Tennessee River adjacent to the 3M Decatur, AL facility in April, 2006 and analyzed for PFOA concentrations.
Remark : Reporting limit (RL) = No information
Result : The range of concentrations of PFOA for 12 sediment samples is between 0.393 and 24.1 ng/g (ppb).
Test substance : PFOA
Reliability : (2) valid with restrictions

04.01.2007 (57)

Type of measurement : concentration at contaminated site
Media : sediment
Concentration :
Method : other

Method : Sediment samples were collected from a contaminated site in The Netherlands (2004-2005).
Remark : Reporting limit was 0.4 ng/g dw
Result : PFOA concentration was 7.0 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA

05.01.2007 (149)

Type of measurement : concentration at contaminated site
Media : other: sediment and suspended matter from fresh water and marine locations
Concentration :
Method : other

Method : Sediment and suspended matter samples were collected from fresh water and marine locations in The Netherlands (2004).
Remark : Reporting limit was 0.4 ng/g dw
Result : PFOA concentration was < RL to 24 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (149)

Type of measurement : other: Environmental Concentration
Media : sediment
Concentration :
Method : other

Method : Sediment collected 2003-2005 from rivers in the Kyoto area and from Osaka, Japan.
Remark : Reporting limit = 0.1 ng/g dw
Result : < 0.1 to 1.2 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (399)

Type of measurement : other: Environmental Concentration
Media : sediment
Concentration :
Method : other

Method : 1981-2001; suspended sediment samples collected at Niagara-on-the-Lake in the Niagara River.
Remark : Reporting limit (RL) = No information
Result : Ca. 80 pg/g (1982)
Ca. 100 pg/g (1987/88)
Ca. 180 pg/g (1992/3)
Ca. 220 pg/g (1995)
Ca. 100 pg/g (2000)
Ca. 290 pg/g (2001)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (423)

Type of measurement : other: Environmental Concentration
Media : sediment
Concentration :
Method : other

Method : Sediment samples collected from the Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 0.09-0.10 ng/g dw
Result : 0.96 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: environmental concentration and concentration at contaminated site
Media : other: sewage sludge
Concentration :
Method : other

Method : PFOA was determined in sewage sludge collected near manufacturing sites in the USA [sites included Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL] and in samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN].
Remark : Reporting limit (RL) = 0.2 ng/g ww

Result : The highest reported concentration of PFOA in sewage sludge was 244 ng/g dry weight in a sample collected near a manufacturing site in the USA [sites included Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL]. The results for 2 of the 8 samples were below the reporting limit (0.2 ng/g dry weight). In samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN], the highest result was 3.1 ng/g wet weight.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : other: sewage sludge
Concentration :
Method : other

Method : PFOA was analyzed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.20 ng/g ww
Result : The PFOA concentration in sewage sludge ranged from the reporting limit (0.20 ng/g ww) to 1.1 ng/g ww.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : other: environmental concentration
Media : other: Sewage sludge
Concentration :
Method : other

Method : PFOA was determined in digested sludge samples from waste-water treatment plants (WWTPs) located throughout the US, including the Pacific northwest, locations in the north- and south-central US, and in the Northeast. Samples were collected from February 1998 through June 2004. All WWTPs included in this study received at least 50% domestic waste.
Remark : Year of sampling = 1998-2004
Reporting limit (RL) = 1 ng/g dw
Result : PFOA concentrations ranged from less than the level of detection to 29.4 ng/g, dry weight.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (318)

Type of measurement : other: environmental concentration
Media : other: sewage effluent
Concentration :
Method : other

Method : PFOA was determined in sewage effluent samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN].
Remark : Reporting limit (RL) = 25 ng/l
Result : Samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN], levels of 40 to 670 ng/L of PFOA were detected.
Test substance : PFOA
Reliability : (4) not assignable

Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : concentration at contaminated site
Media : other: sewage effluent
Concentration :
Method : other

Method : PFOA was determined in sewage effluent collected near manufacturing sites in the USA [Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL].
Remark : Reporting limit (RL) = 25 ng/l
Result : Sewage effluent measurements of PFOA show a high result of 2400 ng/L near a manufacturing site in the USA. Results ranged from 84 to 2400 ng/L at these sites [Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL].
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : other: sewage effluent
Concentration :
Method : other

Method : PFOA was determined in sewage effluent from 3 of the Great Lakes.
Remark : Reporting limit (RL) = No information
Result : PFOA, ranging from 3 to 30 ng/L, was found in sewage effluent from 3 of the Great Lakes.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (547)

Type of measurement : other: environmental concentration
Media : other: Sewage effluent
Concentration :
Method : other

Method : PFOA was analysed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.06 ng/l
Result : In both Norwegian and Finnish effluent samples, PFOA is the predominant constituent. The sewage effluent sample from the Faroe Island is considerably less contaminated. PFOA levels ranged from 1.3 to 23 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: sewage effluent
Concentration :
Method : other

Method : 2003; sewage effluent at Aigawa Ryuiki water disposal site; Osaka area, Japan.
Remark : Reporting limit (RL) = 0.1 ng/l
Result : 67,000 ng/l
Source : Data was taken from SIAR Table 19 (December 12, 2006).

Test substance : PFOA
05.01.2007 (535)

Type of measurement : concentration at contaminated site
Media : other: wastewater treatment plant (WTP) effluent
Concentration :
Method : other

Method : The origin and amount of perfluorooctane surfactants in wastewater treatment systems, and the transformation these compounds may undergo during treatment, were evaluated through measurement and experiment. Influent, effluent, and river water at the point of discharge for a wastewater treatment plant (WWTP) were screened for eight perfluorooctane surfactants.
Remark : Year of sampling = 2004
Reporting limit (RL) = < 2 ng/l
Result : N-EtFOSAA was quantified in influent (5.1 ng/L), effluent (3.6 ng/ L), and river water samples (1.2 ng/L), while PFOS and PFOA were quantified in effluent (26 and 22 ng/L, respectively) and river water (23 and 8.7 ng/L, respectively). Signals for PFOS and PFOA were observed in influent samples, but exact quantitative determination could not be made due to low recoveries of these two compounds in field spike samples. Although the source of PFOS and PFOA observed in WWTP effluents is not clear, two hypotheses were examined: (1) the highly substituted perfluorooctane surfactants that constitute commercially available fabric protectors can be transformed to PFOS and PFOA during biological treatment in wastewater treatment systems, and (2) the end products themselves are directly introduced to WWTPs because they are present as residual in the commercial mixtures. Biotransformation experiments of 96 hours were run to determine whether N-EtFOSE could be transformed to lesser-substituted perfluorooctane compounds in bioreactors amended with aerobic and anaerobic sludge from the sampled plant. At the end of the aerobic biotransformation experiment, N-EtFOSAA and PFOSulfinate were the only two metabolites formed and each accounted for 23 and 5.3% of the transformed parent on a molar basis, respectively. Transformation of N-EtFOSE was not observed under anaerobic conditions. A sample of a commercially available surface protection product from 1994 was analyzed and found to contain six of the targeted perfluorinated surfactants, including PFOS and PFOA.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions
04.01.2007 (105)

Type of measurement : concentration at contaminated site
Media : other: wastewater influent and effluent
Concentration :
Method : other

Method : Samples of influent concentrations of PFOA from the Chambers Works wastewater treatment plant were collected in April and May. Effluent concentrations of PFOA were also sampled directly from the wastewater treatment plant.
Remark : Reporting limit (RL) = No information
Result : The concentrations of the influent samples collected in April and May were 194,000 and 26,000 ng/L respectively. The concentrations of the effluent samples collected in April and May were 475,000 and 279,000 ng/L respectively.
Test substance : PFOA
Reliability : (2) valid with restrictions
05.01.2007 (236)

Type of measurement : concentration at contaminated site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Wastewater from 3M and Dyneon manufacturing operations were treated with physical-chemical and biological treatment. Wastewater treatment effluent and non-contact cooling water samples were collected and (PFOA) concentrations were measured.
Remark : Reporting limit (RL) = 0.082 ng/l
Result : For samples collected in 1998, 1999, 2000, 2001, January-May 2003 PFOA was present at an average concentration of 602,000 766,000 1,028,000 310,000, and 58,000-88,300 ng/l, respectively.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (539)

Type of measurement : other: Environmental Concentration
Media : other: wastewater influent and effluent
Concentration :
Method : other

Method : Specific fluorinated analytes, perfluoroalkyl sulfonates, fluorotelomer sulfonates, perfluorocarboxylates and selected fluorinated alkyl sulfonamides were studied at ten municipal wastewater treatment plants in the Pacific Northwest, Southeast, West, West South Central US, West North Central US, and Northeast.
Remark : Reporting limit (RL) = No information
Result : The flow rates in the ten plants ranged from 11,000 m3/day to 600,000 m3/day. Levels of PFOA in the influent ranged from 1.7 ng/l to 89 ng/l. The effluent concentrations of PFOA ranged from 2.5 ng/l to 97 ng/l.
Test substance : PFOA and specific fluorinated analytes, perfluoroalkyl sulfonates, fluorotelomer sulfonates, perfluorocarboxylates and selected fluorinated alkyl sulfonamides
Reliability : (2) valid with restrictions
04.01.2007 (545)

Type of measurement : other: Environmental Concentration
Media : other: wastewater influent and effluent
Concentration :
Method : other

Method : The effluent waters of six activated sludge wastewater treatment plants in New York State were monitored for PFOA and seven other perfluorinated compounds. All of the six plants received domestic wastewater. All but one of the plants received commercial wastewater and only two plants received industrial wastewater. The flow in the plants varied from a low of 0.4 million gallons per day (MGD) to a high of 25 and 35 MGD.
Remark : Reporting limit (RL) = 2.5 ng/l
Result : The levels of PFOA in the effluent of all six plants ranged from 58 ng/l to 1050 ng/l. Average concentrations of PFOA in the effluent of the two high capacity plants were 135 ng/l and 239 ng/l at the 25 and 35 MGD plants, respectively. The smaller plant average effluent levels ranged from 67 ng/l to 697 ng/l. Concentrations of PFOA in the sludge samples at the two large plants were 69-241 ng/g for the 35 MGD plant and 18-89 ng/g for the 25 MGD plant.
Test substance : PFOA and 7 other perfluorinated compounds
Reliability : (2) valid with restrictions
04.01.2007 (557)

Type of measurement : other: Environmental Concentration at Contaminated Site

Media : other: wastewater effluent
Concentration :
Method : other

Method : Wastewater treatment plant effluent samples from the 3M Cottage Grove, MN facility were analyzed from Outfall SD 001. Samples were collected nine times between January 2000 and June 2003.
Remark : Reporting limit (RL) = No information
Result : Levels of PFOA in the wastewater effluent ranged from a high of 1991 ppb in January 2000 to a low of 16.4 ppb in June 2003. Average effluent levels of PFOA for early 2000 mid, and late 2000 were 1,991,000 ng/l and 216,000 and 180,000 ng/l respectively. The monthly effluent averages for January through June 2003 continued to drop with average monthly levels of 79,000, 79,400, 74,500, 110,500, 98,000, and 17,700 ng/l respectively.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (539)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Two types of water samples were collected at 3M's Guin site.
Remark : Reporting limit (RL) = Ca. 25 ng/l
Result : Water samples analyzed at the 3M facility contained levels of PFOA at a maximum of 10,800 ng/l. Surface water samples contained PFOA levels ranging from <25-10,800 ng/l. Samples from a municipal water pipeline within the facility ranged from <25-9100 ng/l.
Test substance : PFOA, PFBS, PFHS, and PFOS
Reliability : (2) valid with restrictions
04.01.2007 (1)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Industrial effluents of textile and dyeing manufacturers in Chung-Li, Taiwan.
Remark : Reporting limit (RL) = 0.8 ng/l
Result : Not detected to 39 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Effluents of municipal WWTPs near Taipei and Tainan, Taiwan.
Remark : Reporting limit (RL) = 0.8 ng/l
Result : 36-170 ng/l
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Sewage treatment plant final effluent and biosolids.
Remark : Reporting limit (RL) = 1 ng/l (effluent) and 0.1 ng/g dw (biosolids)
Result : 10-34 ng/L (stp effluent)
0.7-13 ng/g dw (biosolids)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (141)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : 2003; effluent of an urban-industrial WWTP in Spain.
Remark : Reporting limit (RL) = 100 ng/l
Result : Mean: < 100 - 1400 ng/L (range: 100 - 4300 ng/L).
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (74)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : 2003; 5 locations in Barcelona harbor, Spain.
Remark : Reporting limit (RL) = 1 ng/l (effluent) and 0.1 ng/g dw (biosolids)
Result : 150 ng/L
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (74)

Type of measurement : other: Environmental Concentration at Contaminated Site
Media : other: wastewater effluent
Concentration :
Method : other

Method : Wastewater from printing plant, electronic production, leather processing, metal processing, paper production, photo graphic laboratory, textile production; Austria.
Remark : Reporting limit (RL) = 50 ng/l
Result : 63-560 ng/l.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (322)

Type of measurement : other: environmental concentration
Media : other: Landfill effluent
Concentration :
Method : other

Method : PFOA was analysed in samples collected from areas in the Nordic countries.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 0.06 ng/l
Result : The range of PFOA in landfill effluents in Nordic countries was 91 to 516 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.
04.01.2007 (347)

Type of measurement : concentration at contaminated site
Media : other: Landfill effluent
Concentration :
Method : other

Method : PFOA was determined in samples collected from a manufacturing site in Parkersburg, WV.
Remark : Limit of detection (LOD) for this procedure is 10 ng/L and the limit of quantitation (LOQ) is 50 ng/L.
Year of sampling = 1994-2003
Result : From a manufacturing site in Parkersburg, WV, the concentrations of PFOA in landfill effluent ranged from 61 to 3,200,000 ng/L.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

03.01.2007 (225)

Type of measurement : concentration at contaminated site
Media : other: Landfill effluent
Concentration :
Method : other

Method : PFOA was determined from landfill effluent samples collected at these manufacturing sites [Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL].
Remark : Reporting limit (RL) = 25 ng/l
Result : Landfill effluent measurements of PFOA ranged from below the detection limit (25 ng/L) to 48,000 ng/L at these manufacturing sites [Decatur, AL; Mobile, AL; Columbus, GA; and Pensacola, FL].
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : other: Landfill effluent
Concentration :
Method : other

Method : PFOA was determined in landfill effluent taken from samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN].
Remark : Reporting limit (RL) = 25 ng/l
Result : In samples collected away from manufacturing sites in the USA [Port St. Lucie, FL and Cleveland, TN], levels of 940 to 1000 ng/L of PFOA were detected.
Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (55)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : A preliminary screening of PFOS and related compounds has been performed in liver samples of fish, birds and marine mammals from Greenland and the Faroe Islands.
Remark : Reporting limit (RL) = 12 ng/g ww

Result : PFOS was the predominant fluorochemical analyzed in the biota. PFOA levels were below the level of detection (12 ng/g).
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (103)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Concentrations of PFOA were determined in marine mammals including bottlenose dolphins (Tursiops truncatus), striped dolphins (Stenella coeruleoalba), common dolphins (Delphinus delphi), fin whales (Balenoptera physalus), long-finned pilot whales (Globicephala melas); in fishes such as northern bluefin tuna (Thunnus thynnus), swordfish (Xiphias gladius); and in common cormorants (Phalacrocorax carbo) collected from Italian coast of the Mediterranean Sea.
Remark : Reporting limit (RL) = 72 ng/g ww
Result : PFOA levels ranged from 29 to 450 ng/g in the cormorant liver; less than the level of detection (72 ng/g) in the Northern bluefin tuna and swordfish liver and blood samples; and from less than the level of detection (2.5 ng/g) to 3.8 ng/g in the dolphin and whale liver, muscle, and samples; and 2.5 ng/ml blood samples.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (138)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : In this study the age related presence of perfluorinated chemicals in blood plasma collected from beef cattle were examined.
Remark : Reporting limit (RL) = 0.010 ng/mL
Result : PFOA levels ranged from less than the level of detection (0.010 ng/mL) to 0.10 ng/mL. In 2 of the 3 cattle, levels increased from 9 to 27 months of age.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (288)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS), perfluorooctanesulfonamide (PFOSA) and perfluorooctanoate (PFOA) were measured in bile, liver, and muscle tissues of several edible fishes including Mugil spp., and in liver, kidney, muscle, brain, spleen, and lungs of pelicans (Pelecanus onocrotalus) collected from Cartagena Bay in Colombia.
Remark : Reporting limit (RL) = No information
Result : PFOA was found in the bile of Mugil sp. at several hundreds of ng/mL.

PFOS concentrations as great as 5600 ng/mL were found in the bile. PFOSA was not found in bile at a detection limit of 3 ng/mL.

Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (341)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Livers of birds collected from Japan and Korea (n = 83) were analyzed to determine the concentrations of perfluorooctanesulfonate (PFOS), perfluorooctanesulfonamide (FOSA), perfluorooctanoic acid (PFOA) and perfluorohexanesulfonate (PFHS).
Remark : Reporting limit (RL) = 19 ng/g ww (Japan) and 36 ng/g ww (Korea)
Result : PFOA and PFHS were found in 5-10% of the samples analyzed. The greatest concentrations of PFOA and PFHS in bird livers were 21 and 34 ng/g, wet weight, respectively. PFOS was found in the livers of 95% of the birds analyzed at concentrations greater than the limit of quantitation (LOQ) of 10 ng/g, wet weight. The greatest concentration of PFOS of 650 ng/g, wet weight, was found in the liver of a common cormorant from the Sagami River in Kanagawa Prefecture. Concentrations of PFOS in bird livers from Japan and Korea were within the ranges of values reported for those from the United States and certain European countries.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (348)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Perfluorooctanesulfonate (PFOS), perfluorooctanesulfonamide (FOSA), perfluorohexanesulfonate (PFHxS), and perfluorooctanoate (PFOA) were detected in 175 samples of liver and blood of bluefin tuna (Thunnus thynnus), swordfish (Xiphias gladius), common cormorants (Phalacrocorax carbo), bottlenose dolphins (Tursiops truncatus), striped dolphins (Stenella coeruleoalba), common dolphins (Delphinus delphi), fin whales (Balenoptera physalus), and long-finned pilot whales (Globicephala melas) from the Italian coast of the Mediterranean Sea and in livers of ringed seals (Phoca hispida), gray seals (Halichoerus grypus), white-tailed sea eagles (Haliaeetus albicilla), and Atlantic salmon (Salmo salar) from coastal areas of the Baltic Sea.
Remark : Reporting limit (RL) = 72 ng/g ww
Result : Mean PFOS concentrations (61 ng/g, wet wt) in cormorant livers collected from Sardinia Island in the Mediterranean Sea were less than the concentrations of PFOA (95 ng/g, wet wt). PFOS concentrations in cormorant livers were significantly correlated with those of PFOA. PFOS was detected in all of the wildlife species analyzed. Concentrations of PFOS in blood decreased in order of bottlenose dolphins > bluefin tuna > swordfish. FOSA was found in 14 of 19 livers or blood samples of marine mammals from the Mediterranean Sea. The highest concentration of 878 ng FOSA/g, wet wt, was found in the liver of a common dolphin. Livers of ringed and gray seals from the Bothnian Bay in the Baltic Sea contained PFOS concentrations ranging from 130 to 1100 ng/g, wet wt. No relationships between PFOS concentrations and ages of ringed or gray seals were observed. Concentrations of PFOS in livers of seals were 5.5-

fold greater than those in corresponding blood.

A significant positive correlation existed between the PFOS concentrations in liver and blood, which indicates that blood can be used for nonlethal monitoring of PFOS. Trend analysis of PFOS concentrations in livers of white-tailed sea eagles collected from eastern Germany and Poland since 1979 indicated an increase in concentrations during the 1990s. Livers of Atlantic salmons did not contain quantifiable concentrations of any of the fluorochemicals monitored. PFOS is a widespread contaminant in wildlife from the Baltic and the Mediterranean Seas, while FOSA and PFOA were detected only in certain locations indicating their sporadic spatial distribution.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (350)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : In this study, perfluorooctanesulfonate (PFOS), perfluoro-octanesulfonamide (FOSA), perfluorohexanesulfonate (PFHxS), and perfluorooctanoate (PFOA) were measured in livers of mink and river otters collected from various locations in the United States.

Remark : Year of sampling = 1995-2000
Reporting limit (RL) = 4.5 ng/g ww (mink) and 7.5 ng/g ww (river otters)

Result : PFOS was found in all mink livers analysed. Frequencies of occurrence of FOSA, PFHxS, and PFOA were less. The greatest concentration of PFOS measured in liver of mink was 5140 ng/g, wet weight. Maximum concentrations of FOSA, PFHxS, and PFOA in mink livers were 590, 39, and 27 ng/g, wet weight, respectively. There were no significant positive relationships between concentrations of PFOS and PFHxS or PFOA in mink livers. Concentrations of PFOS were positively correlated with those of FOSA in mink livers from Illinois. There was no significant correlation between concentrations of PFOS and lipid content in mink livers. There were no age- or sex- related differences in the concentrations of fluorochemicals in mink livers. Greater concentrations are associated with those individuals collected near urbanized and/or industrialized areas. PFOS was detected in livers of all river otters collected from Washington and Oregon at concentrations ranging from 25 to 994 ng/g, wet wt. PFOA concentrations were less than 7.5 ng/g in all samples from rivers in Washington except they were less than 7.5-19 and less than 7.5-11 ng/g from Fort Ward, WA and Silverdale, WA, respectively and less than 7.5 ng/g in all samples from rivers in Oregon except for less than 7.5-19 and less than 7.5-9.9 ng/g in the Willamette River, Oregon and Yaquinia, Oregon Rivers, respectively.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (352)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : This study examined 12 perfluorinated acids in plasma of 73 loggerhead sea turtles (Caretta caretta) and 6 Kemp's ridley sea turtles (Lepidochelys

kempi). Juvenile turtles were captured in two coastal locations: one located in Core Sound, North Carolina and the other in offshore waters of South Carolina, Georgia, and Florida.

Remark : Reporting limit (RL) = No information

Result : Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) were the predominant compounds with respective mean (standard deviation) concentrations of 11,000 (17,200) and 3200 (1500) pg/mL for loggerhead turtles and 39,400 (17,100) and 3570 (550) pg/mL for Kemp's ridley turtles. PFOS concentrations were approximately three- and ten-fold higher than the concentration of the sum of PCB congeners (SPCBs) typically measured in blood of loggerhead and Kemp's ridley turtles, respectively. Perfluorobutanoic acid and perfluoropentanoic acid were not detected in any turtle, while perfluorohexanoic acid, perfluoroheptanoic acid, and perfluorooctanesulfonamide were detected, respectively, in 8%, 12%, and 1% of the loggerhead samples and 0%, 17%, and 0% of the Kemp's ridley samples. Perfluorononanoic acid, perfluorodecanoic acid, perfluorododecanoic acid, perfluoroundodecanoic acid, and perfluorohexanesulfonate respective mean concentrations were 298, 515, 181, 359, and 155 pg/mL in loggerhead plasma and 1650, 2370, 462, 1420, and 253 pg/mL in Kemp's ridley turtle plasma. The Kemp's ridley turtles were found to have significantly higher concentrations of the sum of perfluorinated carboxylic acids (SPFCs) than the loggerhead turtles. Loggerheads captured in inshore waters of NC had significantly higher SPFCs concentrations than loggerheads captured in offshore waters of SC, GA, and FL. SPFC concentrations in loggerhead turtles captured in offshore waters were positively correlated with latitude, with turtles captured further north having higher concentrations. SPFC concentrations in loggerhead turtles also correlated positively with carapace length, suggesting bioaccumulation with age. As expected for juveniles, no sex differences were observed for any PFC measured in the loggerheads from offshore South Carolina, Georgia, and Florida.

Test substance : PFOA

Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (367) (368)

Type of measurement : other: environmental concentration

Media : biota

Concentration :

Method : other

Method : Perfluoroalkyl substances were determined in liver tissues and blood of polar bears (Ursus maritimus) from five locations in the North American Arctic and two locations in the European Arctic. Concentrations of perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), heptadecafluorooctane sulfonamide, and perfluoroalkyl carboxylates (PFCAs) with C8-C15 perfluorinated carbon chains were determined.

Remark : Reporting limit (RL) = 2.3 ng/g ww

Result : PFOS, PFHxS, and PFCAs with chain lengths C8 through C13 (e.g., PFOA) were detected at concentrations above the detection limit at all locations [PFOA limit of detection was 2.3 ng/g ww; PFOA concentrations ranged from less than LOD to less than 57.1 ng/g ww]. PFOS concentrations were significantly correlated with age at four of seven sampling locations, while gender was not correlated to concentration for any compound measured. Populations in South Hudson Bay (2000-2730 ng/g wet wt), East Greenland (911-2140 ng/g wet wt), and Svalbard (756-1290 ng/g wet wt) had significantly higher PFOS concentrations than western populations such as the Chukchi Sea (435-729 ng/g wet wt). Concentrations of perfluorocarboxylic acids (PFCAs) with adjacent chain lengths (i.e., C9:C10 and C10:C11) were significantly correlated, suggesting PFCAs have a common source within a location, but there were differences in proportions of PFCAs between eastern and western location

sources. Concentrations of PFOS in liver tissue at five locations were correlated with concentrations of four polychlorinated biphenyl congeners (180, 153, 138, and 99) in adipose tissue of bears in the same populations, suggesting similar transport pathways and source regions of PFOS or precursors.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (560)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Perfluoroalkyl substances were determined in polar bears (Ursus maritimus) collected in East Greenland to compare with other populations and to examine effects of age and gender on concentrations of these contaminants. Hepatic tissue was analyzed for perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate, heptadecafluorooctane sulfonamide (PFOSA), and perfluoroalkyl carboxylates (PFCAs) with C9-C15 perfluorinated carbon chains.

Remark : Year of sampling = 1999-2001
Reporting limit (RL) = 2 ng/g ww

Result : The mean PFOA concentration in liver samples [n = 29] was 10 ng/g wet weight. Male bears showed a significant increase in concentration up to age six for PFCAs with C10-C14 carbon chains. Significant correlations were found between adjacent chain length PFCAs, (e.g., PFNA to PFDA). This may indicate a common source for these chemicals, although the specifics of source and mode of transport are unknown. No significant correlations were found between concentrations of PFCAs in liver tissue and previously reported polychlorinated biphenyl (PCB) congeners analyzed in fat samples from the same bears. Concentrations of PFOS found in samples from East Greenland (mean = 2470 ng/g wet weight) were similar to Hudson Bay, Canada, and both populations had significantly greater concentrations than those reported for Alaska, suggesting a spatial trend.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (561)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : In September 2002 wood mice (Apodemus sylvaticus) were captured at Blokkersdijk (n = 21) and Galgenweel (n = 21), located in the city of Antwerp, Belgium. Both areas are artificial sand dune habitats with willow (Salix spp.) groves. Sherman live traps were set up at dusk. The trapped animals were brought to the laboratory the next morning. Upon arrival, the animals were anesthetized with ether, and blood was taken using the retroorbital puncture method. Serum was prepared by centrifugation at room temperature (4000 rpm, 5 min) and frozen in liquid nitrogen. After sacrificing the animals, sex, body, and liver weight were determined. The eye lenses were collected and fixed in 10% formaldehyde. The liver was dissected, weighed, and stored in liquid nitrogen for further analysis.

Remark : Reporting limit (RL) = 110 ng/g ww

Result : Perfluorooctanoic acid levels, at both locations, were less than the or equal

to the level of detection (110 ng/g). The liver perfluorooctane sulfonic acid (PFOS) concentrations in the Blokkersdijk mice were extremely high (0.47-178.55 ug/g wet weight). Perfluorononanoic, perfluorodecanoic, perfluoroundecanoic, and perfluorododecanoic acids were found sporadically in the liver tissue of the Blokkersdijk mice. The liver PFOS concentrations at Galgenweel were significantly lower than those at Blokkersdijk (0.14-1.11 ug/g wet weight). Further results suggest sex independence of the liver PFOS levels, increased levels of PFOS bioaccumulation in older mice, and maternal PFOS transfer to the young. Several liver end points were significantly elevated in the Blokkersdijk mice: liver weight, relative liver weight, peroxisomal beta-oxidation activity, microsomal lipid peroxidation level, and mitochondrial fraction protein content. For the mitochondrial fraction catalase activity, no significant difference between locations was found. The liver weight, relative liver weight, and liver microsomal lipid peroxidation level increased significantly with the liver PFOS concentration. No indications for PFOS-mediated effects on the serum triglyceride, cholesterol, or potassium levels were obtained. The liver PFOS concentration was negatively related to the serum alanine aminotransferase activity.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (321)

Type of measurement : other: environmental concentration

Media : biota

Concentration :

Method : other

Method : PFOA was determined in fish and fish-eating water birds, in mink and river otter livers, in oysters, and in surface water, sediments, clams, and fish collected from locations upstream and downstream of the 3M facility at Decatur, AL. Fish were sampled from the U.S., certain European countries, the North Pacific Ocean, and Antarctic locations. Fish-eating bird samples were collected from the U.S., including Midway atoll, the Baltic and Mediterranean Seas, Japanese and Korean coasts. Mink and river otter livers were collected from the U.S.

Remark : Reporting limits were different depending on the sample being tested and the location of where the sample was taken and the test done.

Result : PFOA was rarely found in fish and fish-eating water birds.

PFOA was found in a few mink livers from Massachusetts at a concentration range of <18 to 108 ng/g, dry weight, but not found in mink from Louisiana, South Carolina and Illinois. PFOA concentrations in river otter livers from Washington and Oregon States were less than the quantification limit of 36 ng/g, wet weight.

PFOA was not detected at quantifiable concentrations in oysters collected in the Chesapeake Bay and Gulf of Mexico of the U.S. coast.

The concentrations of PFOA were determined in surface water, sediments, clams, and fish collected from locations upstream and downstream of the 3M facility at Decatur, AL. Of the three downstream water and sediment sampling locations, the two closest to the 3M facility had PFOA surface water concentrations significantly greater than the two upstream sites (means of 1900 ug/L and 1024 ug/L, versus 0.008 (est.) and 0.028 ug/L); the three downstream locations also had sediment concentrations significantly greater than the upstream sites (wet weight means 1855 ug/kg, 892 ug/kg, 238 ug/kg vs. 0.08 (est.) and 0.09 (est.)). The average fish whole body PFOA concentration for the upstream location was 11.7 ug/kg (wet weight), while that for the downstream location was 106.4 ug/kg;

the small sample size prevented determination of significance. The average PFOA concentration in clams at the upstream location was 4.38 ug/kg; that for the downstream location was 8.42 ug/kg. These differences were not significant.

Test substance : PFOA
Reliability : (4) not assignable
Documentation insufficient for assessment

04.01.2007 (274) (275) (277) (278) (279)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : In this study spatial and temporal trends in the concentrations of selected PFCs were measured using archived liver samples of ringed seal (Phoca hispida) from East and West Greenland. The samples were collected in four different years at each location, between 1986 and 2003 in East Greenland and between 1982 and 2003 in West Greenland.
Remark : Reporting limit (RL) = 12 ng/g ww
Result : Perfluorooctanoic acid was not found in detectable concentrations in any sample. PFOS was the major contributor to the burden of PFCs in samples, followed by perfluoroundecanoic acid (PFUnA). Perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) were also detected in most samples. Perfluorohexane sulfonate (PFHxS) and perfluorooctane sulfonamide (PFOSA) were only found sporadically. Regression analysis of logarithmic transformed PFOS, PFDA, and PFUnA median concentrations indicated a significant temporal trend with increasing concentrations at both locations. A spatial trend in PFOS concentrations was observed between the two sampling locations, with significantly higher concentrations in seals from East Greenland.
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (102)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : A screening study was conducted to determine the occurrence, distribution and fate of perfluorinated alkylated substances (PFAS) and related chemicals in the Nordic environment.
Remark : Year of sampling = 2003-2004
Reporting limit (RL) = 1 ng/g ww
Result : A screening study on occurrence, distribution and fate of perfluorinated alkylated substances (PFAS) and related chemicals in the Nordic environment revealed an ubiquitous distribution of perfluorinated contaminants. The Nordic biota samples showed signals of species dependent distribution and levels. Highest PFAS levels were found in top predating Danish harbour seal (Phoca vitulina) samples with PFOS as predominant PFAS contaminant. PFOA concentrations were much lower ranging from below the level of detection to as high as 5.6 ng/g. In Faroe Island pilot whales (Globicephala melas), PFOSA and PFOS were dominating with up to 364 ng/g wet weight. Also Finnish and Norwegian pike samples (Esox lucius) are highly contaminated with PFOS (PFOS = 551 ng/g ww) demonstrating that also the freshwater ecosystem is contaminated with PFAS related chemicals. The patterns found in biota point towards both country specific release patterns and species depended up-take/ accumulation properties. The fact that PFOS and PFOSA were

also detected in anadromous Arctic char in the Faroe Islands indicates that long-range transport in air and/or precipitation is occurring.

Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals.

04.01.2007 (347)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : A suite of analytical tools were employed to characterize fish (common shiner, Notropus cornutus) and surface water samples collected following the discharge of fire retardant foam containing perfluorinated surfactants that subsequently entered into Etobicoke Creek, a tributary to Lake Ontario.
Remark : Reporting limit (RL) = 1.2 ng/g ww
Result : Total perfluorocarboxylate (5-14 carbons) concentrations ranged from 0.07 to 1.02 ug/g. Total perfluoroalkanesulfonate (4, 6, and 8 carbons) concentrations in fish liver samples ranged from 2.00 to 72.9 ug/g. PFOA concentrations ranged from 6.0 to 91 ng/g ww. Upstream of the spill, 88 ng/g ww were found in the liver of the common shiner.

In addition to fish samples, total perfluoroalkanesulfonate (6 and 8 carbons) concentrations were detected in creek water samples by LC/MS/MS over a 153 day sampling period with concentrations ranging from <0.017 to 2260 ug/L; perfluorooctanoate creek concentrations (<0.009-11.3 ug/L) were lower than those observed for the perfluoroalkanesulfonates.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (445)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : The concentrations of perfluorinated organochemicals (FOCs) were determined in marine mammals stranded along the southern North Sea coast. The presence of FOCs in top predators such as marine mammals would suggest a potential biomagnification of these compounds and their widespread occurrence. Liver and kidney tissues were sampled from nine marine mammal species stranded along the southern North Sea coast.
Remark : Year of sampling = 1995-2000
Reporting limit (RL) = 110 ng/g ww
Result : PFOA concentrations were less than the limit of detection (110 ng/g) in any of the species. Among all the measured FOCs compounds, PFOS (perfluorooctane sulfonate) was predominant in terms of concentration. The highest PFOS concentrations were found in the liver of harbor seal compared to white-beaked dolphin, harbor porpoise, gray seal, sperm whale, white-sided dolphin, striped dolphin, fin whale, and hooded seal. PFOS concentrations differed significantly between sexes and age classes in harbor porpoises.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (609)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : To provide a preliminary assessment of fluorinated contaminants, including perfluorinated carboxylic acids (PFCAs), in the Canadian Arctic, polar bears, ringed seals, arctic fox, mink, common loons, northern fulmars, black guillemots, and fish were collected at various locations in the circumpolar region.
Remark : Reporting limit (RL) = 2.0 ng/g ww
Result : PFOA concentrations were less than the level of detection (2.0 ng/g) in liver samples from trout, lake whitefish, artic sculpin, northern pike, and white sucker; in the common loon, northern fulmar, and black guillemot; in the mink, fox, and ringed seal. Mean PFOA concentrations in the liver samples from polar bears were 8.6 ng/g (range of 2.9 to 13 ng/g). PFOS was the major contaminant detected in most samples and in polar bear liver was the most prominent organohalogen (mean PFOS = 3.1 ug/g wet weight) compared to individual polychlorinated biphenyl congeners, chlordane, or hexachlorocyclohexane-related chemicals in fat. Using two independent mass spectral techniques, it was confirmed that all samples also contained ng/g concentrations of a homologous series of PFCAs, ranging in length from 9 to 15 carbons. Sum concentrations of PFCAs were lower than total PFOS equivalents in all samples except for mink. In mink, perfluorononanoate (PFNA) concentrations exceeded PFOS concentrations.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (432)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Isomer profiles of perfluorinated carboxylic acids (PFCAs) were determined in liver samples of 15 polar bears (Ursus maritimus) from the Canadian Arctic and eastern Greenland.
Remark : Reporting limit (RL) = No information
Result : The PFOA isomer pattern in Greenland polar bear samples showed a variety of branched isomers while only the linear PFOA isomer was determined in Canadian samples.
Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (147)

Type of measurement : other: environmental concentration
Media : biota
Concentration :
Method : other

Method : Perfluorooctanesulfonate (PFOS) and other fluorinated organic contaminants were measured in the tissues of wildlife, including, fish, birds, and marine mammals. Some of the species studied include bald eagles, polar bears, albatrosses, and various species of seals. Samples were scanned for four FOCs: PFOS, perfluorooctane sulfonylamide (PFOSA), perfluorohexane sulfonate (PFHS), and perfluorooctanoate (PFOA).
Remark : Reporting limits were different depending on the sample being tested and

the location of where the sample was taken and the test done.

Result : All concentrations of PFHS were less than the LOQ (LOQ range = 1 to 86 ng/g, wet wt) and only a few samples contained PFOA or PFOSA at levels greater than the LOQ of 2.5 to 180 ng/g, wet wt, and 1 to 38 ng/g, wet wt, respectively.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (276)

Type of measurement : other: environmental concentration

Media : biota

Concentration :

Method : other

Method : Temporal trends in the concentrations of PFOS and PFOA in the Baltic Sea marine environment were measured using archived guillemot eggs. Samples collected from Stora Karlso (Sweden) between 1968 and 2003 were received from an environmental specimen bank and concentrations of PFOS and PFOA were analyzed.

Remark : Reporting limit (RL) = 3 ng/g ww

Result : PFOA was not detected in any of the samples (LOD 3 ng/g), but there was an almost 30-fold increase in PFOS concentrations in the guillemot eggs during the time period, from 25 ng/g in 1968 to 614 ng/g in 2003 (wet weight). Regression analysis indicated a significant trend, increasing on average between 7 and 11% per year. A sharp peak in PFOS concentrations was observed in 1997 followed by decreasing levels up to 2002, but this cannot be linked to the PFOS phase-out, which occurred at the end of this period.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

04.01.2007 (323)

Type of measurement : other: Environmental Concentration

Media : other: domestic animals (cattle, chicken, pig, and horse)

Concentration :

Method : other

Method : Serum and liver samples of domestic animals (cattle, chicken, pig, and horse); Japan

Remark : Reporting limit (RL) = 49 pg/ml sera and 49 pg/g liver

Result : Serum:
50 pg/mL (cattle)
<49-965 pg/mL (chicken)
176 pg/mL (pig)
<49 pg/mL (horse)
liver:
<49-239 pg/g (cattle)
<49 pg/g (chicken)
<49-300 pg/g (pig)

Source : Data was taken from SIAR Table 19 (December 12, 2006).

Test substance : PFOA

05.01.2007 (287)

Type of measurement : other: Environmental Concentration

Media : other: beaver liver

Concentration :

Method : other

Remark : RL = 0.01-0.08 ng/g ww
Result : 0.28-0.29 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (588) (589)

Type of measurement : other: Environmental Concentration
Media : other: birds
Concentration :
Method : other

Method : 2004; glaucous gull liver samples collected from the marginal ice zone in the Barents Sea; Norway.
Remark : Reporting limit (RL) = 0.128 ng/g ww
Result : < 0.128 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (87)

Type of measurement : other: Environmental Concentration
Media : other: birds
Concentration :
Method : other

Method : Liver of mallard and black-headed gull sampled from shallow water at Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : < 3 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: birds
Concentration :
Method : other

Method : 2004; brown pelicans were collected in Cartagena Bay (Colombia) and tissue and organs investigated.
Remark : Reporting limit (RL) = 30 ng/g ww
Result : 182 ng/g ww (spleen)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (466)

Type of measurement : other: Environmental Concentration
Media : other: Pandas
Concentration :
Method : other

Method : PFOS and PFOA levels in serum of the giant panda and the red panda were taken in animals captured in zoos and animals parks from six provinces in China.
Remark : Reporting limit (RL) = No information
Result : The PFOA level ranged from 330 to 8200 ng/l for the red panda and from 320 to 1560 ng/l for the giant panda. Greater concentrations of the fluorochemicals were found in panda sera for those individuals collected from zoos near urbanized or industrialized areas than other areas.
Test substance : PFOA and PFOS
Reliability : (2) valid with restrictions
04.01.2007 (144)

Type of measurement : other: Environmental Concentration
Media : other: freshwater fish
Concentration :
Method : other

Method : Channel catfish and large mouth bass were collected from the Ohio River near the Washington Works, DuPont WVA site and analyzed for APFO and PFOA in filet, viscera and carcass. Fish of the same species were also caught in a background area for comparison of contaminant levels.
Remark : Reporting limit (RL) = No information
Result : Channel catfish filet PFOA levels ranged from 0.237 ng/g to 9.19 ng/g and large mouth bass filet ranged from 0.234 ng/g to 1.67 ng/g. Viscera of the channel catfish ranged from a low of 5.88 ng/g to a high of 1440 ng/g. The large mouth bass viscera was measured between 1.23 ng/g and 70.7 ng/g. Carcass PFOA levels for channel catfish fell between 0.412 (non-quantifiable) and 10.8 ng/g. Carcasses of the large mouth bass contained between 0.412 (non-quantifiable) and 2.39 ng/g of PFOA. The background for channel catfish and large mouth bass filet ranged from 0.146 (non-quantifiable) - 1.65 ng/g ; the viscera background was 0.85 - 42.6 ng/g; and the carcass background was 0.087 (non-quantifiable)- 1.59 ng/g.
Test substance : APFO and PFOA
Reliability : (2) valid with restrictions
04.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : other: freshwater fish
Concentration :
Method : other

Method : Two species of freshwater fish were collected from the vicinity of the 3M Decatur, AL facility in December, 2004. Channel catfish and large mouth bass were collected from upriver and cross river Tennessee River locations, Baker's Creek mouth and outfall, Fox Creek and downriver at Mallard Creek. The filet and whole body parts were both analyzed for PFOA.
Remark : Reporting limit (RL) = No information
Result : PFOA levels in channel catfish filets upriver ranged from non-detect to 5.88 ng/g. PFOA levels in filets and whole body samples of channel catfish cross river from the Decatur, AL facility were non-detect. All samples of large mouth bass filets and whole body samples upriver and cross river were non-detect. Baker's Creek PFOA levels for channel catfish filets and whole body samples ranged from non-quantifiable to 5.68 ng/g; the large mouth bass at this location ranged from non-quantifiable to 6.06 ng/g. PFOA levels in channel catfish and large mouth bass were much lower at Fox Creek with the range for both filets and whole body from non-quantifiable to 0.774 ng/g. Downriver at Mallard Creek the two species of fish varied more. Channel catfish were non-detect or non-quantifiable for all samples; large mouth bass filets ranged from non-detect to 0.588 ng/g and whole body samples from non-detect to 4.01 ng/g.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : other: freshwater fish
Concentration :
Method : other

Method : 2001-2003; Liver samples from smallmouth and largemouth bass collected in New York State, USA.
Remark : Reporting limit (RL) = 1.5 ng/g ww
Result : < 1.5-7.7 ng/g ww

Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (555)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : Liver and muscle samples of coastal fish (tilapia) and liver samples of Japanese seaperch; Taiwan.
Remark : Reporting limit (RL) = 10 ng/g dw
Result : Liver samples

120 ng/g dw (tilapia; mean)
340 ng/g dw (seaperch; mean)

Muscle samples

100 ng/g dw (tilapia; mean)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : 2002-2003; cod samples (blood) collected from the Gulf of Gdansk, Baltic Sea (Poland)
Remark : Reporting limit (RL) = 0.05 ng/ml (blood)
Result : < 0.05-0.73 ng/mL
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (286)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : 2005; fish (scad, jack mackerel, sand fish, trout, sardine) were purchased in retail shopping markets and liver samples investigated; Japan.
Remark : Reporting limit (RL) = 2.5 ng/g ww
Result : < 2.5-10 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (399)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : Liver samples of fish (filefish, sea bream, red sea bream, right eye flunder, hammerhead shark collected from shallow water at Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : < 3-15 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA

05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : Liver of herbivore mudskipper collected from tidal flat at Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : < 3 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : Liver of omniivore mudskipper collected from tidal flat at Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : < 7.8 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: Salt-water fish
Concentration :
Method : other

Method : 2003; mullet (Mugil incilis) were collected along the north coast of Colombia (3 locations) and tissue and organs investigated.
Remark : Reporting limit (RL) = 50 ng/ml (bile)
Result : < 50-370 ng/ml (bile).
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (466)

Type of measurement : other: Environmental Concentration
Media : other: clams
Concentration :
Method : other

Method : Asiatic clams were collected from the same locations as freshwater fish at the 3M Decatur, AL site in December, 2004. Upriver, cross river, Baker's Creek, Fox Creek and Downriver Mallard Creek locations were the sampling locations.
Remark : Reporting limit (RL) = No information
Result : The PFOA concentrations in clams upriver were non-quantifiable. The cross river level of PFOA was 0.508 ng/g. Baker's Creek PFOA levels were 0.720 and 1.01 ng/g. Fox Creek clams contained 0.508 ng/g of PFOA and Mallard Creek clams had 0.582 ng/g of PFOA.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : other: oyster tissue
Concentration :

Method : other

Method : 2004; Oyster tissue samples collected from Tokyo Bay, Japan.
Remark : Reporting limit (RL) = 0.204 ng/g ww
Result : 660 pg/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (564) (565)

Type of measurement : other: Environmental Concentration
Media : other: Oysters
Concentration :
Method : other

Method : Muscle samples were collected from oyster (Crassostrea gigas) culture sites in Chi-Ku coastal area; Taiwan.
Remark : Reporting limit (RL) = 10 ng/g ww
Result : 130-160 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration
Media : other: Oysters
Concentration :
Method : other

Method : Viscus samples were collected from oyster (Crassostrea gigas) culture sites in Chi-Ku coastal area; Taiwan.
Remark : Reporting limit (RL) = 10 ng/g ww
Result : 130-180 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (602)

Type of measurement : other: Environmental Concentration
Media : other: Oysters, mussels, and clams
Concentration :
Method : other

Method : Soft tissue of oyster, mussel, and clam collected at tidal flat from Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : 6.0-9.5 ng/g dw
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: dolphins
Concentration :
Method : other

Method : The environmental distribution and the biomagnification of a suite of perfluoroalkyl compounds (PFCs), was investigated in the food web of the bottlenose dolphin. Dolphin tissue samples and surficial seawater were collected at Sarasota Bay, Florida and Charleston Harbor, South Carolina.
Remark : Reporting limit (RL) = No information
Result : Dolphin plasma PFOA concentrations for Sarasota averaged 3.4 ng/l; plasma for Charleston averaged 43 ng/l. The Sarasota sea water PFOA average level was 3.6 ng/l; Charleston was 9.5 ng/l. From these measurements a trophic magnification factor (TMF) for the Charleston

Harbor area was calculated of 13 plus or minus 22 for dolphin plasma. On a whole dolphin burden basis the TMF for Charleston Harbor dolphin is 6.3 plus or minus 6.7.

Test substance : PFOA and other perfluoroalkyl compounds
Reliability : (2) valid with restrictions
04.01.2007 (328)

Type of measurement : other: Environmental Concentration
Media : other: bottlenose dolphin
Concentration :
Method : other

Method : 2003, blood samples from bottlenose dolphin collected in the Gulf of Mexico and the Atlantic Ocean along the coast of the USA
Remark : Reporting limit (RL) = 0.5 ng/g ww
Result : 0.7-26 ng/g ww - Sarasota Bay
0.6-0.9 ng/g ww - Bermuda
1-70 ng/g ww - Indian River Lagoon
4.6-163 ng/g ww - Charleston
20-115 ng/g ww - Delaware Bay
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (329)

Type of measurement : other: Environmental Concentration
Media : other: Harbor porpoises liver tissue
Concentration :
Method : other

Method : Harbor porpoises liver tissue; sampled as by-caught from coastal waters; Iceland, Norway, Denmark, German Baltic Sea.
Remark : Reporting limit (RL) = 62 ng/g ww
Result : 62 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (608)

Type of measurement : other
Media : other: porpoise
Concentration :
Method : other

Method : Liver of finless porpoise sampled from shallow water at Ariake Sea, western Japan
Remark : Reporting limit (RL) = 3 ng/g ww
Result : 9.1 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: mussel tissue
Concentration :
Method : other

Method : 2004; Mussel tissue samples collected from six locations along the east coast of China.
Remark : Reporting limit (RL) = 0.204 ng/g ww
Result : < 204-328 pg/g ww.
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (564) (565)

Type of measurement : other: Environmental Concentration
Media : other: polar bears
Concentration :
Method : other

Method : 1972-2002; polar bear liver tissue samples collected from two geographic locations in the North American Arctic (eastern group: northern Baffin Island, Canada; western group: Barrow, Alaska.
Remark : Reporting limit (RL) = 2.3 ng/g ww
Result : Eastern group:
ca. 3 ng/g ww (1972)
ca. 20 ng/g ww (2002)
Western group:
ca. 2 ng/g ww (1972)
ca. 5 ng/g ww (2002)
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (562)

Type of measurement : other: Environmental Concentration
Media : other: polar bear liver
Concentration :
Method : other

Remark : Reporting limit (RL) = No information
Result : 10 - 110 ng/g ww (value refers to PFOA and/or PFNA; not further specified).
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (249)

Type of measurement : other: Environmental Concentration
Media : other: harbor seals
Concentration :
Method : other

Method : 2002; Harbor seals stranded along The Netherlands coastline of the Wadden Sea were collected and organs and tissues analyzed (liver, kidney, blubber, muscle, tracheo-branchial muscle, and spleen).
Remark : Reporting limit (RL) = 62 ng/g ww
Result : < 62 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (608)

Type of measurement : other: Environmental Concentration
Media : other: Hispid cotton rats
Concentration :
Method : other

Method : Small mammal sampling was conducted concurrently with vegetation sampling from October 5-7, 2004 at the 3M Decatur, AL facility. Hispid cotton rats were collected in the same areas as the sampled vegetation. Livers and serum were collected from each rat and analyzed for PFOA.
Remark : Reporting limit (RL) = 400 ng/ml
Result : PFOA was present above the 400 ng/ml detection limit in two of the fifteen sampled rat serum samples but below the quantitation limit of 1000 ng/ml. All liver samples measured non-detect for PFOA.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : other: worm samples
Concentration :
Method : other

Method : Worm samples (whole body) collected from Ariake Sea, western Japan.
Remark : Reporting limit (RL) = 3 ng/g ww
Result : 82 ng/g ww
Source : Data was taken from SIAR Table 19 (December 12, 2006).
Test substance : PFOA
05.01.2007 (452)

Type of measurement : other: Environmental Concentration
Media : other: Plants
Concentration :
Method : other

Method : The 3M Decatur, AL facility collected vegetation in its former sludge application area and background locations on October 7, 2004. Eleven samples of four different species and two unidentified species were sampled in four separate sludge application fields. Seven samples were taken in a sludge application control area and a background area of the same four vegetative species found in the sludge application areas; broomsedge, pokeweed, curly dock, and goldenrod.
Remark : Reporting limit (RL) = No information
Result : PFOA concentrations in the vegetation in the former sludge application fields ranged from 42.3 - 912 ng/g (ppb). In the sludge control and the background area the PFOA concentrations ranged from 1.99 - 9.22 ng/g (ppb).
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (57)

Type of measurement : other: Environmental Concentration
Media : other: Grass
Concentration :
Method : other

Method : Grass (Canada bluegrass and Kentucky bluegrass) samples were collected from on-site at the Washington Works DuPont West Virginia site. PFOA measurements were made of samples of unwashed grass, grass washed with laboratory distilled water and the water used to wash the grass.
Remark : Reporting limit (RL) = No information
Result : The on-site unwashed grass samples collected at Washington Works contained PFOA levels between 154 and 574 ng/g (ppb) on a dry weight basis. Washed grass samples had measured PFOA levels of between 33.5 and 92.8 ppb on a dry weight basis. The grass washwater contained PFOA ranging between 6.6 ppb and 24 ppb. The washwater prior to being used to wash the grass contained no PFOA at a detection limit of 0.0039 ppb. Samples were also collected of the upper 0"-1" and 1-3" soil/grass and soil/root zones which contained some amounts of grass material. The 0"-1" zone contained between 24.2 and 134 ppb of PFOA. The 1"-3" zone contained PFOA levels from 28.6-69.6 ppb.
Test substance : PFOA
Reliability : (2) valid with restrictions
04.01.2007 (240)

Type of measurement : other: Environmental Concentration
Media : other: Grass
Concentration :
Method : other

Method : Grass (Canada bluegrass and Kentucky bluegrass) samples were collected from off-site of the Washington Works DuPont West Virginia site within a two mile radius of the site. These grass samples were collected during two contrasting periods of precipitation one dry, and one wet. The wet collection period followed a rain duration of at least ? inches (Need this info).

Remark : Reporting limit (RL) = No information

Result : The grass samples collected during the dry period at the 0"-1" depth had measured levels of PFOA between <5.21 (non-quantifiable) ppb to 118 ppb. The grass root material collected during the dry period between 1"-6" in depth contained PFOA at <5.5 (non-quantifiable) to 63.2 ppb. The wet sample soil/grass 0"-1" PFOA levels in grass roots and soil were between <5.21 ppb(non-quantifiable) and 126 ppb. The wet sample PFOA soil/grass levels in grass roots and soil were measured at <7.29 (NQ) ppb to 55 ppb.

Test substance : PFOA

Reliability : (2) valid with restrictions

04.01.2007 (240)

Type of measurement : background concentration

Media : other: PFC Polymers

Concentration :

Method : other

Method : Chiantore et al (2000) investigated the photochemical stability of the low fluorine content (CF3 moieties) poly(2,2,2-trifluoroethyl methacrylate) [PTFEMA], and copolymers of high fluorine content (n-C8F17 moieties) 1H,1H,2H,2H-perfluorodecyl methacrylate [XFDMA] with 2-ethylhexyl methacrylate [EHMA] under artificial solar irradiation. The degree of photodegradation was determined by weight loss and gel content, size exclusion chromatography and FTIR spectroscopy.

Result : There was a low extent of chain scission in PTFEMA which was exposed up to 2000 hours whereas the two XFDMA-EHMA copolymers exhibited greater degradation, extensive cross-linking, formation of low-molecular weight products and oxidation reactions. They suggest that the fast formation carboxylic acid groups may be due to an intramolecular cyclic elimination of alkyl side groups involving hydrogen atoms in the gamma position. Although of interest with respect to potential biodegradation of polymeric chemistries, the relevance for this SIAR is questionable because the material tested is not a commercial material, and no evidence of degradation of the fluorinated functionality is shown.

Test substance : poly(2,2,2-trifluoroethyl methacrylate) [PTFEMA], and copolymers of high fluorine content (n-C8F17 moieties) 1H,1H,2H,2H-perfluorodecyl methacrylate [XFDMA] with 2-ethylhexyl methacrylate [EHMA]

Reliability : (2) valid with restrictions

16.01.2007 (118)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Remark : The octanol-water partition coefficient Kow cannot be determined for the surface active PFOA or APFO.

29.12.2006

3.3.2 DISTRIBUTION

Remark : The octanol-water partition coefficient Kow cannot be determined for the surface active PFOA or APFO. Calculating the distribution between environmental compartments with models using Kow (for example the Mackay model) is not applicable.

29.12.2006

Media : water - soil
Method : other (measurement): Adapted from EPA OPPTS 835.1220
Year : 2000

Method : APFO was determined in peat moss, upstream sediment, East Wood soil, garden area soil, kaolin clay, sand, montmorillonite clay, downstream sediment, and sassafras soil.

Result : Of the nine materials tested, five of them (peat moss, upstream sediment, East Wood soil, garden area soil, and kaolin clay) exhibited significant adsorption at one or more of the added concentrations of APFO. Peat moss alone, however, adsorbed a significant amount at all three concentrations of added APFO; 50, 500, and 5000 ug APFO/L. Kaolin clay adsorbed a significant amount of APFO at 500 and 5000 ug APFO/L. The garden area soil adsorbed a significant amount of APFO at 500 ug APFO/L. Upstream sediments from the Ohio River and East Wood soil adsorbed a significant amount of APFO at 50 ug APFO/L only. Sand, montmorillonite clay, downstream sediment, and sassafras soil did not adsorb a significant amount of APFO at any concentration of the added APFO.

Once adsorbed on peat moss, most of the APFO (>76%) did not desorb after two washings with a solution of 0.01M CaCl2. For the kaolin clay, most the APFO adsorbed when added at 5000 ug APFO/L desorbed with washing (>60%). At APFO added at 500 ug APFO/L, however, an average of 98% did not desorb from the kaolin clay after two washings. The East Wood soil, which adsorbed 46% of the APFO added at 50 ug APFO/L desorbed only about 2%. For the garden area soil 57% of the APFO desorbed when adsorbed from the 500 ug APFO/L solution. No measurable desorption of APFO from the upstream sediment after two washings was observed when the APFO was added at 50 ug APFO/L.

Summary: Five of the nine materials appeared to adsorb a significant amount of APFO added at one or more concentrations of APFO. For four of the five materials to which APFO significantly adsorbed, most of the adsorbed APFO appeared not to desorb after 2 washings at one or more concentrations of added APFO.

Conclusions: Low adsorption to clay, sand, soil, and sediment; High mobility in soil; High adsorption to peat moss.

Test substance : APFO
Reliability : (1) valid without restriction
Comparable to guideline study

29.12.2006 (207)

Media : water - soil
Method : OECD Guide-line 106
Year : 2003

Method : The adsorption of APFO was determined in four soil samples (Drummer, Hidalgo, Cape Fear, and Keyport) and in one activated sludge sample (Wilmington sludge).

Result : The average adsorption of APFO during a 24-hour equilibration time at a

1:1 solution ratio ranged from 40.8% for the Hidalgo soil to 81.8% for the Drummer soil. The test soils yielded adsorption coefficient (Kd) values of 4.25 to 8.86 mL/g for the Drummer soil, 1.82 to 4.26 mL/g for the Keyport soil, 1.19 to 2.84 mL/g for the Cape Fear soil, and 0.41 to 0.83 mL/g for the Hidalgo soil. The Wilmington sludge sample had the highest Kd value of 22.5 mL/g, with Kd values that ranged from 12.6 to 36.8 mL/g.

The adsorption coefficient as a function of organic carbon (Koc) values of the soils ranged from 48.8 mL/g for the Keyport soil to 229 mL/g for the Cape Fear soil and the adsorption coefficient as a function of organic matter (Kom) values ranged from 28.4 mL/g for the Keyport soil to 133 mL/g for the Cape Fear soil. The Wilmington sludge sample had an average Koc value of 36.5 mL/g and average Kom value of 21.2 mL/g.

Conclusions: Low adsorption to soil and sludge; High mobility in soil.

Test substance : APFO
Reliability : (1) valid without restriction
GLP guideline study (OECD)

29.12.2006 (78)

Media : water - soil
Method : other (measurement): Mobility in soil per EPA pesticide regulation requirements
Year : 1978

Method : 25 mL solutions (5.2 to 523 mg/l) of radiolabeled FC-143 were shaken for 24 hours with 5 g of Brill sandy loam soil (57% sand, 36% silt, 7% clay, 2.5% organic matter, and 1.5% organic carbon). After the adsorption step, 22.5 mL of each solution was recovered; therefore it was assumed that 2.5 mL of the liquid remained with the soil. Desorption extraction was performed with water after the adsorption phase of the experiment. Scintillation counting was used to determine the FC-143 in the soil and water from the desorption extraction.

Result : The adsorption coefficient (K) for FC-143 was determined to be 0.38 indicating FC-143 would be judged mobile in the sandy loam soil used in this study [a recalculation by EPA showed K = 0.21 and Koc = 14 with the same conclusion as to high mobility].

Test substance : APFO
Reliability : (4) not assignable
Documentation insufficient for assessment

29.12.2006 (27)

Media : water - air
Method : other (measurement)
Year : 1993

Method : Impinger studies were performed to examine the volatility of APFO and PFOS. Solutions of APFO or PFOS containing ammonium acetate in water/1-propanol (50:50) or phase transfer agents, e.g., n-alkyldimethyl-benzylammonium chloride were blown with 280 liters of air at a flow rate of 1 L/min.

Remark : These results were reviewed by Dr. Edwin Tucker of the Chemistry Dept. at the University of Oklahoma. He concluded that it is very unlikely that these fluorochemicals were removed by bubbling air through water due to their very low vapor pressures. He suggested that a more plausible mechanism for loss from the solution phase is concentration of the surfactants in foam and loss from the bubbled solutions as foam or micro-droplets. In the second part of the experiment, air was passed over the fluorochemicals and bubbled through a train of impingers containing the ammonium acetate solution. It was expected that if any fluorochemicals were present in the air they would be transferred and retained by the ammonium acetate solution. However, no fluorochemicals were present in either the first or second

impinger.

Result : The results indicate there is some loss of APFO and PFOS, but most of the solutions retained over 80% or more of the fluorochemicals. The average retention was 92% for both APFO and PFOS. This indicates that there is loss from the solutions. However, some of the solutions, particularly the n-alkyldimethylbenzylammonium chloride solution, appear to retain all the fluorochemicals.

Test substance : APFO and PFOS

Reliability : (4) not assignable
Documentation insufficient for assessment

29.12.2006 (47)

3.4 MODE OF DEGRADATION IN ACTUAL USE

Memo : Thermal stability of PTFE and FEP

Method : Investigation of the thermal stability of PTFE and FEP at 360 and 500°C and varying levels of fuel load and oxygen.
(FEP: polymer of tetrafluoroethylene and hexafluoropropylene, formula [(CF(CF3)-CF2)x(CF2-CF2)y]F; melting point range 245-280°C, melt processible. supplied in the form of translucent pellets, powder, or as an aqueous dispersion)

Result : Approximately 50 ppm PFOA and C6 perfluorocarboxylic acid each were detected from the thermal degradation of FEP at 500°C (no findings (LOD not noted) from PTFE).

Reliability : (2) valid with restrictions

29.12.2006 (408)

Memo : Degradation in air of TFE homopolymer

Method : Weight-loss data have been obtained with a thermogravimetric analyzer for the degradation in air of tetrafluoroethylene (TFE) homopolymer, its copolymers with hexafluoropropylene (HFP) and perfluoropropylvinyl ether (PPVE), and for TFE/ethylene/perfluorobutylethylene terpolymer. The evolved gases were detected and quantified by IR.

Result : At typical polymer processing temperatures the amount of the hourly weight loss rate is below 0.5% (maximum processing temperature: up to 3.2%). The gaseous degradation product is mainly COF2.

None of the six polymers studied showed any detectable weight loss (<0-0.5%/hour) at their continuous use temperature; but three had weight losses at their maximum processing temperatures that were greater than l%/hour.

Reliability : (2) valid with restrictions

29.12.2006 (80)

3.5 BIODEGRADATION

Type : aerobic

Inoculum : activated sludge

Contact time :

Degradation : (±13) % after 28 day(s)

Result :

Deg. product :

Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"

Year : 1997

GLP : no

Test substance : as prescribed by 1.1 - 1.4

Method : Modified Strum Test (OECD 301 B). In this test, biodegradability was measured as CO2 evolution. Activated sludge was used as the inoculum.

Result : Ammonium perfluorooctanoate (30% solution) did not demonstrate "Ready Biodegradability." Note that failure to pass a "Ready Biodegradability Test" does not imply that the test substance will persist in the environment for an extended period of time. The toxicity test, which included both the test substance and the reference chemical (sodium benzoate) in the same flask, yielded < 25% biodegradation within 14 days; therefore, ammonium perfluorooctanoate was considered inhibitory to microorganisms in the inoculum.

Test substance : APFO

Reliability : (2) valid with restrictions
Guideline study without GLP

29.12.2006 (203)

Type : aerobic

Inoculum Contact time : activated sludge

Degradation : (±0) % after 18 day(s)

Result :

Deg. product :

Method : EPA OPPTS 835.3200

Year : 2001

GLP : no

Test substance : as prescribed by 1.1 - 1.4

Method : In this study, perfluorooctanesulfonyl-based substrates were individually incubated with aerobic sludge for eighteen days at a concentration of approximately 2.5 pg/mL.

Result : Activated sludge was collected from a municipal wastewater treatment plant in St. Paul, MN. APFO was not measurably degraded after 18 days; this test is typically conducted for 28 days - 18 days may be viewed as insufficient time to induce conditions needed for potential biodegradation.

Reliability : (2) valid with restrictions
Guideline study without GLP

29.12.2006 (56)

Type : aerobic

Inoculum :

Deg. product :

Method : other: EPA Standard Method 507/508A

Year : 1987

GLP : no

Test substance : as prescribed by 1.1 - 1.4

Method : BOD analysis was performed in accordance with EPA Standard Method #507 while COD analysis was performed in accordance with EPA Standard Method #508A. This test was conducted for 20 days.

Result : BOD results were unexpectedly high due to impurities in the APFO sample (estimated to be 78-93%); Biodegradation results are inconclusive.

Test substance : APFO; purity was not specified.

Reliability : (2) valid with restrictions
GLP guideline study with acceptable restrictions

29.12.2006 (42)

Type : aerobic

Inoculum : other: aerobic bacteria

Deg. product :

Method : other

Year : 1996

GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Biodegradability bottle tests were conducted with aerobic bacteria previously shown to have a broad range of degradative capabilities.
Result : Inconclusive because the analytical analysis lacked sensitivity.
Test substance : APFO
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

20.01.2006 (201)

Type : aerobic
Inoculum Deg. : activated sludge
product :
Method : other: Shake culture test modeled after the Soap and Detergent Association's presumptive test for determination of ABS/ALS biodegradability
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The Shake Culture study was modeled after the Soap and Detergent Association's presumptive test for the determination of ABS/LAS biodegradability.
Result : Activated sludge was collected from a manufacturing facility in Decatur, AL, and from a municipal wastewater treatment plant in St. Paul, MN. No biodegradation of APFO was observed in the 2.5-month study. However, the LAS control, which is typically readily biodegradable, seemed at first sight not to show appreciable biodegradation until day 37. But actually in the 4th growth period (day 10-13), phenol was used as reference compound with sufficient degradation (30 mg/l to below 1.3 mg/l).
After this, starting with growth period 5, LAS as reference compound was tested. In growth period 5, 6, and 7 (each lasting 3 days) the freshly added LAS in each growth period was not sufficiently removed. In growth period 8 (lasting 6 days) starting at day 22, 91% LAS removal occurred within this 6 days. Therefore pass level of the reference (control) substance is reached.
Test substance : APFO
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

29.12.2006 (28)

Type : aerobic
Inoculum : domestic sewage
Deg. product :
Method : other: Laboratory scale reactors for aerobic treatment
Year : 2004
GLP : no data
Test substance : other TS

Method : Determination of fluorinated surfactants and their metabolites in sewage sludge samples by liquid chromatography with mass spectrometry and tandem mass spectrometry after pressurized liquid extraction and separation of fluorine-modified reversed-phase sorbents. Wastewater was spiked with 5 mg/L PFOA. Analytical monitoring showed no minimization of the PFOA concentration during aerobic treatment by metabolic (primary degradation) or mineralization processes. Time of monitoring is not mentioned. Comparison to anaerob degradation experiments suggest at monitoring time of 25 days. The LOD for PFOA is not mentioned. Calibration curves for PFOA (after separation with LC on RP-C8) is linear over a range of 2-25 ug/ml.

Result : No biodegradation was observed.
Test substance : PFOA
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment

29.12.2006 (437) (543)

Type : aerobic
Inoculum : activated sludge, domestic
Deg. product :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : The biodegradation of 3-14C, 1H,1H,2H,2H-perfluoro-1-decanol [14C-8-2 FTOH] was investigated in mixed bacterial culture and activated sludge. 14CO2 and 14C-organic volatiles in the headspace of the sealed bottles and bottles with continuous air flow were analyzed up to 4 months. After sample extraction with acetonitrile, 14C-labeled biotransformation products (metabolites) were quantified by LC/ARC (on-line liquid chromatography/accurate radioisotope counting) and identified by quadruple time-of-flight (Q-TOF) mass spectrometry and GC/MSD (mass selective detector).
Result : Three metabolites not yet reported in the literature have been identified as CF3(CF2)6(14)CHOHCH3 (7-2 sFTOH), CF3(CF2)6(14)CH=CHCOOH (7-3 unsaturated acid or 7-3 u acid), and CF3(CF2)6(14)CH=CHCONH2 (7-3 u amide) along with five previously reported metabolites [CF3(CF2)6(14)CF2CH2CHO (8-2 FTAL), CF3(CF2)6(14)CF2CH2COOH (8-2 acid), CF3(CF2)6(14)CF=CHCOOH (8-2 u acid), CF3(CF2)6(14)CH2CH2COOH (7-3 acid), and CF3(CF2)6(14)COOH (PFOA)]. No CF3(CF2)6(14)CF2COOH (14C-PFNA) was observed, suggesting that alpha-oxidation does not take place. It was found that strong adsorption to the activated sludge and subsequent transformation, even under continuous air flow, greatly reduced partitioning of 8-2 FTOH or any transformation products to air. CF3(CF2)4COOH (PFHA; perfluorohexanoic acid) was observed and increased in mixed bacterial culture over 28 days and accounted for about 1% of the initial 14C-8-2 FTOH concentration from day 28 to day 90. 14CO2 accounted for 1% of initial 14C in activated sludge with continuous air flow at day 1 and increased over time. In closed bottles, 14CO2 in the headspace of activated sludge medium increased to 12% of the available 14C over 135 days with periodic addition of ethanol, as compared to 3% when no additional ethanol was added. These results show that replenishment of organic carbon enhanced microbial mineralization of multiple--CF2--groups in the fluorocarbon chain of 14C-8-2 FTOH. At day 90 the net increase of fluoride ion in the mixed bacterial culture was 93 ug/L, equivalent to 12% of total mineralization (destruction) of the 14C-8-2 FTOH. These results demonstrate that perfluorinated carbon bonds of 14C-8-2 FTOH are defluorinated and mineralized by microorganisms under the conditions of the test, forming shorter fluorinated carbon metabolites.
Test substance : 8:2 Telomer Alcohol (1H,1H,2H,2H-perfluoro-1-decanol)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

29.12.2006 (621)

Type : aerobic
Inoculum Deg. : activated sludge, domestic
product :
Method : other
Year : 2005

GLP : no data
Test substance : other TS

Method : The biodegradation potential of 3-(14)C-1H,1H,2H,2H-perfluorodecanol [14C-labeled 8-2 telomer B alcohol or 14C-labeled 8-2 TBA] was investigated by diluted activated sludge from a domestic wastewater treatment plant under aerobic conditions. After sample extraction with acetonitrile, biotransformation products were separated and quantified by LC/ARC (on-line liquid chromatography/accurate radioisotope counting) with a limit of quantification about 0.5% of the 14C counts applied to the test systems. Identification of biotransformation products was performed by quadrupole time-of-flight mass spectrometry.

Result : Three transformation products have been identified: CF3(CF2)6(14)CF2CH2COOH (8-2 saturated acid); CF3(CF2)6(14)CF=CHCOOH (8-2 unsaturated acid); and CF3(CF2)6(14)COOH (perfluorooctanoic acid, PFOA), representing 27, 6.0, and 2.1% of the initial 14C mass (14C counts applied) after 28 days, respectively. A transformation product, not yet reported in the literature, has also been observed and tentatively identified as CF3(CF2)6(14)CH2CH2COOH (2H,2H,3H,3H-perfluorodecanoic acid); it accounted for 2.3% of the mass balance after 28 days. The 2H,2H,3H,3H-perfluorodecanoic acid is likely a substrate for beta-oxidation, which represents one of the possible pathways for 8-2 telomer B alcohol degradation. The 8-2 saturated acid and 8-2 unsaturated acid cannot be directly used as substrates for beta-oxidation due to the proton deficiency in their beta-carbon (C3 carbon) and their further catabolism may be catalyzed by some other still unknown mechanisms. The 2H,2H,3H,3H-perfluorodecanoic acid may originate either from the major transformation product PFOA or from other unidentified transformation products via multiple steps. Approximately 57% of the starting material remained unchanged after 28 days, likely due to its strong adsorption to the PTFE septa of the test vessels. No perfluorononanoic acid was observed, indicating that alpha-oxidation of CF3(CF2)6(14)CF2CH2COOH did not occur under the study conditions. Several 14C-labeled transformation products that have not yet been identified (each less than 1% of the mass balance) were also observed and together accounted for 7% of the total 14C mass balance after 28 days. It is not clear whether these unidentified transformation products were resulting from further metabolism of 8-2 saturated acid or 8-2 unsaturated acid. The results suggest that perfluorinated acid metabolites such as PFOA account for only a portion of the transformation products observed. Also, the observed volatility and bioavailability of 14C-labeled 8-2 TBA for microbial degradation was markedly decreased as a result of the presence of a strongly adsorbing matrix such as
PTFE in the experimental systems. It is apparent that the biological fate of 8-2 telomer B alcohol is determined by multiple degradation pathways, with neither beta-oxidation nor any other enzyme-catalyzed reactions as a single dominant (principal) mechanism under the study conditions.

Test substance : 8:2 Telomer Alcohol (1H,1H,2H,2H-perfluoro-1-decanol)
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

29.12.2006 (622)

Type : aerobic
Inoculum : activated sludge
Deg. product :
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Activated sludge was collected from a manufacturing facility and biodegradation was monitored for up to 20 days.
Result : Based on BOD, no biodegradation was observed after 20 days. COD data was questionable. Weight of evidence - no biodegradability.
Test substance : APFO
Reliability : (3) invalid
Significant methodological deficiencies

29.12.2006 (33)

Type : aerobic
Inoculum Contact :
time :
Degradation : (±0) % after 5 day(s)
Result :
Deg. product :
Method : other
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Biodegradation (BOD/COD/TOC).
Result : Study was inconclusive because unexpectedly high BODs were found. This may be indicative of impurities or other quality issues with this study.
Test substance : APFO
Reliability : (4) not assignable
Documentation insufficient for assessment

20.01.2006 (26)

Type : aerobic
Inoculum : activated sludge
Deg. product :
Method : other
Year : 1985
GLP : no
Test substance : other TS

Method : Activated sludge were collected from a manufacturing facility. Biodegradation was observed after 20 days.
Result : The biodegradation determination based on BOD/COD ratios was difficult to interpret due to the COD methods apparently yielding incomplete oxidation resulting in the BOD values being greater than the COD values [typically, COD for raw domestic wastewater is about 2.5 times the 5-day BOD]. Days 10 and 20 were more than 7x COD.
Test substance : PFOA
Reliability : (3) invalid
Significant methodological deficiencies

20.01.2006 (38)

Type : aerobic
Inoculum :
Deg. product :
Method : other: Aquatic mesocosm
Year : 2001
GLP : no data
Test substance : other TS

Method : Aquatic mesocosms were dosed with concentrations of PFOA ranging from 0.3 to 100 ppm and the persistence in the water column and degradation were determined.
Result : Persistent in water column; No significant degradation after 35 days.
Test substance : PFOA

Reliability : (4) not assignable
Documentation insufficient for assessment

20.01.2006 (515)

Type : anaerobic
Inoculum : domestic sewage
Deg. product :
Method : other: Laboratory scale reactors for anaerobic treatment.
Year : 2004
GLP : no data
Test substance : other TS

Method : The biochemical degradation of PFOA was monitored under anaerobic conditions in closed-loop systems. Adsorptive effects to glass and polypropylene were also examined. LC-MS under negative electrospray conditions was applied for determination. Effluent from a stabilization tank of sewage treatment plant sludge was used for degradation tests. Wastewater was spiked with 5 mg/L PFOA. LOD for PFOA is not mentioned. Calibration curves for PFOA (after separation with LC on RP-C8) is linear over a range of 2-25 ug/ml.
Remark : Personal communication of the author (Schroeder, June 26th 2005): the result (PFOA no longer detected after 25 days) is a consequence of analytical deficiencies.
Result : PFOA was no longer detected after 25 days but no increased concentrations of fluoride ions were observed; no adsorption on glass walls of reactor; results indicate potential transformation of COO- but whereabouts of perfluorinated segment was not determined.
Test substance : PFOA
Reliability : (3) invalid
Not reliable, significant methodological deficiences

29.12.2006 (437) (543)

Deg. product :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : Perfluorinated chemicals (PFCs) form a special category of organofluorine compounds with particularly useful and unique properties. Their large use over the past decades increased the interest in the study of their environmental fate. Fluorocarbons may have direct or indirect environmental impact through the products of their decomposition in the environment. It is a common knowledge that biodegradation is restricted within non-perfluorinated part of molecules; however, a number of studies showed that defluorination can readily occur during biotransformation. To evaluate the fate of PFCs in the environment a set of principal transformations was developed and implemented in the simulator of microbial degradation using the catabolite software engine (CATABOL). The simulator was used to generate metabolic pathways for 171 perfluorinated substances on Canada's domestic substances list.
Result : It was found that although the extent of biodegradation of parent compounds could reach 60%, persistent metabolites could be formed in significant quantities. During the microbial degradation a trend was observed where PFCs are transformed to more bioaccumulative and more toxic products. Perfluorooctanoic acid and perfluorooctanesulfonate were predicted to be the persistent biodegradation products of 17 and 27% of the perfluorinated sulphonic acid and carboxylic acid containing compounds, respectively.
Test substance : PFOA
Reliability : (2) valid with restrictions
Accepted calculation method

13.01.2006 (154)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	28 day(s) at °C
Concentration	:	50 µg/l
BCF	:	3.1
Elimination	:	no data
Method	:	OECD Guide-line 305
Year	:	2000
GLP	:	yes
Test substance	:	other TS
Method	:	The test method is essentially that of OECD 305. Carp were exposed to either 5 or 50 ug/L of PFOA for 28 days. Analysis was performed on water and fish extracts using LC-MS. No depuration experiment was performed.
Result	:	Exposure concentrations of 5 and 50 ug/L were used. The BCF value for the 50 ug/L concentration was 3.1. For the 5 ug/L concentration, the maximum BCF was determined as 9.4 after 16 days; this level reduced to 5.1 or less by 28 days.
Test substance	:	PFOA
Reliability	:	(1) valid without restriction GLP guideline study (OECD)

20.01.2006 (145)

Species Exposure	:	Oncorhynchus mykiss (Fish, fresh water)
period	:	32 day(s) at 12 °C
Concentration	:	
BCF	:	4
Elimination	:	
Method	:	other
Year	:	2003
GLP	:	no data
Test substance	:	other TS
Method	:	Juvenile rainbow trout (Oncorhynchus mykiss) were exposed in a flow-through system for 12 days to a 1000-fold dilution of a stock solution containing a homologous series of perfluoroalkyl carboxylates and sulfonates (PFAs) followed by a 33-day depuration period in clean water. A stock solution was prepared by first dissolving PFAs in a small amount of methanol, which was subsequently dissolved in 30 L of reverse-osmosis laboratory water. The resulting solution was stirred in a polypropylene container for three days before beginning of the experiment. Two days before test start fish were transferred to glass aquaria lined with polypropylene bags (to avoid binding of test substance onto glass surface). Initial loading was 8 g/L in exposure tanks and 2.5 g/L in control tanks. Fish growth was monitored every 2 to 3 days throughout the study. A peristaltic pump delivered the stirred stock solution into the dilution stream of the treatment tank at 0.5 mL/minute. After 4.5, 9 and 18 hours and 1.5, 3, 6 and 12 days, 3 fish from the exposure tank and one from the control were sampled during the uptake phase. During depuration phase, 3 fish from the exposure tank and one from the control tank were collected after 4.5, 9 and 18 hours and 1.5, 3, 6, 12, 19 and 33 days.

Sampled fish were anesthetized, a blood sample (50-200 µl) was drawn, and fish were euthanized with a blow to the head and cervical dislocation. The gut (esophagus, stomach, pyloric ceca, spleen and intestines) was removed but not analyzed. The blood, carcass and liver samples were analyzed to determine the kinetics of uptake and depuration.

Carcass and liver concentrations were determined using liquid chromatography/tandem mass spectrometry, and kinetic rates were calculated to determine compound-specific bioaccumulation parameters.

For tissue distribution study four immature trout (30-48g) were exposed in a separate tank under the same uptake conditions as the bioconcentration fish. On day 12, 3 fish were randomly sampled and anesthetized. Blood samples were immediately drawn and fish were euthanized with a blow to the head and cervical dislocation. Fish were subsequently dissected to separate and remove spleen, heart, liver, gall bladder, gonads, gills (bones removed), adipose tissue (separated from pyloric ceca) and kidney. A small sample of white muscle was also removed.

Result : One fish (2%) died during uptake phase. No statistically difference was found in the rate of growth for exposed fish relative to controls. No statistically significant difference was found between the liver somatic index of exposed and control fish. PFOA concentration was greatest in blood > kidney > liver > gall bladder and lowest in the gonads > adipose > muscle tissue. Within the blood, the plasma contained between 94 and 99% of total PFOA, with only a minor amount detectable in the cellular fraction. Recovery from hearts and spleen was low (<10%). Visual observation of depuration data indicated possible biphasic depuration in blood, liver and carcass. However, this could not be demonstrated statistically because of the small sample size.

The following BCFs are calculated:

BCFcarcass = 4.0 (+- 0.6); depuration half-life: 5.2 d (+- 0.67)
BCFblood = 27 (+- 9.7); depuration half-life: 4.5 d (+- 1.6)
BCFliver = 8.0 (+- 0.59); depuration half-life: 3.9 d (+- 0.28)

Test substance : 98% PFOA

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific prinicples, and is acceptable for assessment.

20.01.2006 (429)

Species Exposure : Oncorhynchus mykiss (Fish, fresh water)
period : 34 day(s) at °C
Concentration :
Elimination :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : Juvenile rainbow trout (Oncorhynchus mykiss) were simultaneously fed a diet containing a homologous series of perfluoroalkyl carboxylates and sulfonates for 34 days, followed by a 41-day depuration period. The diet contained 0.42 mg PFOA/kg food).

Spiked food was prepared by adding starter food to a round bottom flask containing a solution of the test compound in methanol. The flask was placed in a rotary evaporator and the mixture was slowly dried under vacuum. The resulting spiked food was further dried at 60°C for 3 hours to remove excess methanol. Control food was prepared in the same manner, minus PFOA.

At day 4, 7, 14, 21, 28 and 34 of the uptake period and day 7, 14, 21, 28, 34 and 41 of the depuration phase, fish were collected from the treatment and control tanks. Sampled fish were anesthetized and then euthanized with a blow to the head and cervical dislocation. The gut (esophagus, stomach, pyloric ceca, spleen and intestines) was removed to avoid contamination of carcass with feces and unabsorbed food. The carcass and liver samples were analyzed throughout the experiment to determine the kinetics of uptake and depuration.

Carcass and liver concentrations were determined by using liquid chromatography/tandem mass spectrometry, and kinetic rates were calculated to determine compound-specific bioaccumulation parameters.

The liver somatic index was determined, because PFAs are known to cause hepatomegaly in rodents via peroxisome proliferation.

Result : No mortality occurred in the exposed and control fish, and no significant difference was observed in growth rate for exposed fish relative to controls.

No statistically significant difference was found between the liver somatic index of exposed and control fish.

The carcass uptake curves clearly showed by visual inspection, that the slope of the curve levels off by the end of the uptake period.

The estimated time to achieve steady state was 10 days. A depuration half-life time of 3 days (+- 0.42) and a BAF of 0.038 (+- 0.0062) was determined.

Test substance : 98% PFOA

Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principals, and is acceptable for assessment.

20.01.2006 (430)

Species Exposure : Pimephales promelas (Fish, fresh water)
period : 13 day(s) at 20 °C
Concentration : 25 mg/l
BCF : 1.8
Elimination : yes
Method : other
Year : 1995
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The uptake and depuration test was conducted using a static (test solutions were not renewed) exposure system. During the uptake phase of the experiment, fish were exposed for 13 days to dilution water to which a selected concentration of PFOA had been added. Following the uptake phase, fish were transferred to a dilution water which did not contain added PFOA for a 15-day depuration phase. A control treatment, in which fish were exposed to dilution water to which PFOA had not been added, was included with the test. The control provided a measure of acceptability of the test by giving an indication of the test fish, and the suitability of the dilution water, food, test conditions, and handling procedures. During both phases of the experiment, fish and water samples were removed periodically from the test chambers and analyzed for PFOA.

Remark : Depuration period was 15 days

Result : Perfluorooctanoate (PFO) concentrations increased in the fish tissues over the course of exposure. While the concentration decreased over the period of the clearance phase, the time required for complete removal was longer than the 15 days used in the test. Relative to the control fish, the survival and growth of the test fish exposed to PFO were not adversely affected

during the experiment.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

20.01.2006 (48)

Species Exposure : Lepomis macrochirus (Fish, fresh water)
period : 21 day(s) at °C
Concentration :
Elimination :
Method : other
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A study was conducted to determine if bluegill sunfish bioaccumulate fluorochemicals from the 3M Decatur plant. Two lots of 30 fish were used. One lot was exposed to Decatur plant effluent for 21 days and the other to river water only for 23 days. Exposed fish, both living and dead, as well as the control fish were homogenized and analyzed for fluorochemicals by GC, TLC, and GC/MS.

Result : There were no detectable amounts of APFO in the ethyl acetate or toluene extracts of the tissues. No fluorochemicals were detected in the river water exposed fish. However, interpretation of this study is problematic for several reasons. Effluent concentrations of subject fluorochemicals were not characterized and the specific protocol for exposure of the fish was not found. There was also no information on analysis of the Tennessee River water or effluent used in the study. Additionally, it was not known if there was any opportunity for the depuration of the fish prior to sacrifice. No explanation was attempted as to what was the cause of the twelve dead fish in the effluent-exposed group. The study also did not differentiate between the bioaccumulation of the test compound and the sorption onto the surface of the fish.

Reliability : (3) invalid
Interpretation of this study is problematic for several reasons. Effluent concentrations of subject fluorochemicals were not characterized and the specific protocol for exposure of the fish was not found. There was also no information on analysis of the Tennessee River water or effluent used in the study. Additionally, it was not known if there was any opportunity for the depuration of the fish prior to sacrifice. No explanation was attempted as to what was the cause of the twelve dead fish in the effluent-exposed group. The study also did not differentiate between the bioaccumulation of the test compound and the sorption onto the surface of the fish.

20.01.2006 (3)

Species Exposure : other: Food web from Lake Ontario
period : at °C
Concentration :
Elimination :
Method : other
Year : 2004
GLP : no
Test substance : other TS

Method : Species sample collection:
- Adult lake trout were collected overnight using nylon gillnets with stretched mesh sizes of 7.5-11.5 cm (equivalent to commercial mesh sizes of 3.0-4.5 in.) in 30 to 40 m of water at various locations and years in Lake Ontario.
- Forage fish species, including sculpin, smelt, and alewife, were collected with a modified 9 m Biloxi bottom trawl towed at depths of 80-100 m on

October 9th 2002 at an offshore site near Niagara-on-the-Lake, Lake Ontario.
- Samples of Mysis and Diporeia were collected with a modified epibenthic sled towed at depths of 50-80 m at the same time and location as forage fish.

Storage:
All fish samples were frozen on dry ice immediately after collection and remained frozen until time of processing. Mysis and Diporeia were immediately sorted from the detritus and other arthropods using fine forceps and stored in solvent rinsed metal containers on dry ice as composite samples of greater than 100 individuals per sample.
Adult lake trout samples were homogenized and stored in the Great Lakes Fisheries Specimen Bank (GLFSB). Lake trout homogenates were stored at -20°C (1980-1998) or -80°C (2001) in sealed glass containers. This collection was accessed in 2002 to acquire archived lake trout from Lake Ontario to examine the temporal trend of PFOS contamination. Seven samples were selected per year (i.e. 7 individual fish samples per year) for the years 1980, 1983, 1986, 1989, 1992, 1995, 1998, and 2001.

Sample Preparation:
The invertebrates (Mysis and Diporeia) and the forage fish alewife (mean fish weight = 26.9 g, 2 fish per composite; n=6), smelt (mean fish weight = 9.0 g, 5 fish per composite; n=6), and sculpin (mean fish weight = 9.7 g, 3 fish per composite, n=5) were processed as composites of whole individuals, whereas all lake trout samples analyzed represented individual whole fish homogenates.
Forage fish were prepared by rinsing each fish in distilled water and combining them in steel beakers by cutting each fish into small pieces with clean scissors. The contents of each beaker were then homogenized. Pooled homogenates were then frozen until analysis in clean glass containers lined with clean aluminum foil.
For archived lake trout homogenates, a subsample (1-2 g) of the wet homogenate was weighed and then dried at 70 °C for 3 days in a drying oven.
Invertebrate samples required no sample preparation. One composite invertebrate sample was available for each of Diporeia and Mysis, and these were analyzed in triplicate by subsampling.

Chemical analysis:
Quantitative instrumental analysis was performed by liquid chromatography/tandem mass spectrometry (LC/MS/ MS). The detector was a Micromass Ultima (Micromass, Manchester, UK) triple quadrupole mass spectrometer equipped with an electrospray source operating in negative ion mode. Data were acquired by tandem mass spectrometry using a multiple reaction monitoring (MRM) method.

The method detection limit was 2 ng/g.

Remark : The trophic status of the Lake Ontario food web was elucidated in 1995 using stable isotopes. The relative trophic status, using nitrogen stable isotopes, was Mysis and Diporeia (macroinvertebrates > alewife, smelt, sculpin (forage fish) > lake trout (top predator).

The data indicate that lake trout consume only about 2% sculpin in their diet, with the balance made up of alewife (90%) and smelt (7%).

The feeding preference of the forage fish examined in this study varies greatly among species. In general, alewife feed predominantly on plankton, including cladocerans and cyclopoid copepods, but occasionally on Mysis and Diporeia. Smelt feed mostly on a combination of Mysis and Diporeia but are also piscivorous and have been known to prey upon juvenile sculpin (<25 mm) and young of the year alewife or smelt. Sculpin are

predominantly benthic feeders and Diporeia are their major food source in Lake Ontario, while Mysis represent only a minor source.

Result : Mean concentration of PFOA in whole body homogenates of invertebrates and fish collected from Lake Ontario (2001):

(ng/g wet weight +- SD)

Diporeia	90 ± 8.5
sculpin	44 ± 12
Mysis	2.5 ± 0.4
alewife	1.6 ± 1.5
smelt	2.0 ± 1.1
trout	1.0 ± 0.1

Diporeia occupy the lowest trophic level of all species analyzed in this study. Therefore, it is unusual and counterintuitive that such a species should be the most heavily contaminated organism in the food web with respect to perfluoroalkyl contaminants. Sculpin contamination is resultantly high because Diporeia are its dominant food source. Given that Diporeia is a benthic invertebrate species, and sculpin feed mainly in the benthic environment, this contamination profile may be considered a benthic contamination source signature for this food web.
The concentration of PFOA in Mysis and alewife were an order of magnitude lower than in Diporeia or sculpin. Given the similar feeding habits of these two species (i.e. primarily planktivores), this contamination could be considered a pelagic contamination source signature.
Lake trout and rainbow smelt PFOA concentrations were similar among both species. The contamination profiles in lake trout and rainbow smelt is intermediate to the pelagic and benthic source signatures and probably reflects the feeding habits of these two species which include a combination of pelagic and benthic organisms.

Food Web Biomagnification:
BAFs were calculated for lake trout relative to each of its prey items by dividing the mean wet weight concentration in lake trout by the mean wet weight concentration of the forage fish. However, to account for the abundance of each forage fish in the diet of lake trout (90% alewife, 7% smelt, 2% sculpin), a diet weighted BAF was calculated:

	Trout/prey BAF
lake trout / alewife:	0.63
lake trout / smelt: lake	0.5
trout / sculpin:	0.02
lake trout / prey (weighted) :	0.41

The BAFs < 1 indicate a low bioaccumulation potential.
The Trophic Magnification Factor (TMF) for PFOA was calculated to be 0.58, which also indicates a low biomagnification potential.

Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented and is acceptable for assessment

07.12.2006 (433)

Species Exposure : other: Benthic foodweb from Great Lakes
period : at °C
Concentration :
Elimination :
Method : other
Year : 2005
GLP : no
Test substance : other TS

Method : Species sample collection and preparation:
Biotic samples were collected from several rivers in Michigan and in the

Calumet River in Indiana, USA, during 1998-2001.
Benthic algae, amphipods, zebra mussels, crayfish, round gobies, and smallmouth bass were collected from various locations within 1 km of the Raisin River mouth to Lake Erie, and from the St. Clair River at its confluence with the Belle River, at Marine City, and at Algonac, Michigan. The benthic organisms were also collected from the Calumet River at its confluence with Lake Michigan in Indiana. All of the biotic samples were collected during July to November, 1998 and 1999. Water samples were collected from the St. Clair and Raisin Rivers in 2001 at the locations where benthic organisms had been collected. No water samples were collected from the Calumet River. A few higher trophic-level fishes such as Chinook salmon, lake whitefish, brown trout, and carp were also collected from Michigan waters in 1999 and 2000.
Several hundred zebra mussels were collected from rocky substrata at each location. Fishes were collected by seining or by electroshocking. Amphipods were collected by turning over rocks and using forceps to collect individual organisms. Benthic algae were collected by scraping hard surfaces with a clean toothbrush (for nonfilamentous forms), or by hand-picking tufts of filamentous algae.

Skinless fillets were analyzed for smallmouth bass, whereas the whole body was analyzed for round gobies. Soft tissues of zebra mussels were analyzed. Tissues from several individuals per species (including fish) were pooled to obtain an adequate mass for extraction. Length of each individual fish was measured immediately after collection, and individuals were pooled on the basis of sizes for analysis.
Liver and egg samples were obtained from the higher trophic-level fishes for analysis. Muscle tissue was analyzed for carp.
Plasma from snapping turtles collected from Lake St. Clair, in June 1999, was analyzed. All of the turtles were adults. A large mass of eggs was found in all female turtles.
Livers from adult green frogs collected in 1998 from the vicinity of Calkins Dam on the Kalamazoo River in southwestern Michigan were analyzed.
Livers were analyzed from mink collected by trappers from the Kalamazoo River watershed in 2000-2001.
Carcasses of bald eagles that were found dead in the Upper Peninsula of Michigan in 2000 were collected by or submitted to Rose Lake Wildlife Research Center, Lansing, Michigan. Samples of liver, muscle, fat, kidney, and gallbladder (from nondecomposed carcasses) were wrapped in solvent-cleaned aluminum foil and stored at -20°C until analysis. The gallbladder was filled with bile when collected.

Chemical analysis:
Tissue samples of fish, mussel, amphipods, and algae were analyzed by a solid-phase extraction (SPE) method. Bald eagle liver, kidney, muscle, testes, ovaries, and gallbladder were analyzed using an ion-pair extraction method. Similarly, livers and eggs of Chinook salmon and lake whitefish, muscle tissue of carp, eggs of brown trout, livers of frog and mink, and plasma of snapping turtles were analyzed by the ion-pair extraction method.

Water samples were analyzed following the SPE method.

Quantitative analyses were performed by monitoring a single product ion selected from a primaryion characteristic of a particular fluorochemical using HPLC-ES/MS/MS.

Remark : Trophic transfer of PFOA and other related perfluorinated compounds was examined in a Great Lakes benthic foodweb including water - algae - zebra mussel - round goby - smallmouth bass. In addition, perfluorinated compounds were measured in livers and eggs of Chinook salmon and lake whitefish, in muscle tissue of carp, and in eggs of brown trout. Similarly, green frog livers, snapping turtle plasma, mink livers, and bald eagle

tissues were analyzed to determine concentrations in higher trophic-level organisms in the food chain.

Result : Concentration of PFOA in water:

Raisin River 14.7 ng/l
St. Clair River 4.4 ng/l (4.0-5.0)

Concentration of PFOA in all tissue samples were below limit of quantification. Therefore no bioaccumulation and biomagnification factor could be estimated.

Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented and is acceptable for assessment

07.12.2006 (353)

Species Exposure : other: Trachemys scripta elegans, Chinemys reevesii (reptiles, turtles)
period : at °C
Concentration :
Elimination :
Method : other
Year : 2006
GLP : no
Test substance : other TS

Method : Trachemys scripta elegans (N = 46) and Chinemys reevesii (N = 51) were captured with baited traps in the Ai River (located in Settsu city, Japan), one of its branches, and other uncontaminated sites from September to October 2003 and April to June 2004.

Sample Preparation:
After capture, we recorded the body weight, sex, age, and carapace length of each turtle. Their ages were determined using the rings (annuli) on their scales based on the assumption that only one ring or annulus is formed annually. Blood samples were collected by heart puncture through the plastron. Serum was separated from the red blood cells and other cellular components by centrifugation at 3000 rpm for 5 min. All serum samples were stored at -20°C until use.
Water samples were collected simultaneously from each location when turtles were captured. At each site, two 2-L samples were collected in disposable polyethylene terephthalate containers with a narrow-mouth bottle top and a screw cap as previously reported. We collected surface water samples from the Ai River in the Settsu City and Kyoto areas of Japan. To minimize the possibility of sample contamination, containers were thoroughly rinsed with methanol and deionized water prior to use. All samples were stored at -20°C prior to analysis.

Chemical analysis:
Prior to extraction, the internal standard (1H,1H,2H, 2H-tetrahydroperfluorooctane sulfonate) was added to each sample. For surface water samples, solid-phase extraction was employed. For serum samples, an extraction process developed by Hansen et al. (2001; Environ. Sci. Technol. 36, 1681-1685) was employed. Each extracted solution was analyzed by liquid chromatography/mass spectrometry (LC/MS).

Statistics:
Analysis of covariance was used to determine whether sex, age, species, and log(PFOA level in water) influenced the BCFs of PFOA. Sex, age, species, log(PFOA level in water), and the interaction between these variables were used as independent variables, and the BCFs of the perfluorinated chemicals were used as the dependent variable. $P<0.05$ was considered to be significant. All statistical analyses were carried out using SAS software. Samples that were under the LOQ were deleted from the

statistical analysis.

Result : The extracted standard curves obtained in the range 0.2-500 ng/mL PFOA for serum and 0.1-500 ng/L of PFOA for water showed linearity, with a coefficient of correlation invariably greater than 0.999. The within- and between- day precision and accuracy parameters were found to be precise (CV <7.5%) and accurate (range 98-104%) in water samples and precise (CV <9.2%) and accurate (range 96-107%) in serum samples for both analytes. The mean extraction recovery was always more than 93% in water samples and more than 95% in serum samples. 0.2 ng/ml for serum and 0.1 ng/l for water were assumed to be LOQ, the CV of which was less than 9%.

The PFOA level in water ranged from 16.7 to 87,100 ng/L, and reached its maximum level at the Aigawa Ryuiki water disposal site. Repeated measurements of PFOA levels in the Ai River demonstrated similar ranges of concentrations for these compounds. These results were also consistent with a previous investigation (Saito et al., 2004; Occup. Health 46, 49-59).

Turtle serum levels of PFOA ranged up to 115.6 ug/l and were found to bioconcentrate the PFOA by an average (geometric mean) factor of 3.2, with a range of BCFs from 0.8 to 15.8. Serum concentrations of PFOA from 94 turtles in Japan ranged from 0.3 to 115.6 ug/l.

As the distribution of BCFs did not follow a normal distribution and showed a skewed pattern, not the arithmetic mean but the geometric mean (GM) and geometric standard deviation (GSD) were used for analysis. PFOA was observed in almost all serum samples (91/94 samples). The PFOA level ranged from 16.7 to 87,100 ng/L in water, but from <0.2 to 870 mg/L in serum. The GM (GSD) of the BCF of PFOA was 3.2 (7.9)

The BCF of PFOA showed a large deviation. Bivariate analysis of the BCF of PFOA and the PFOA level in surface water was performed. The BCF of PFOA decreased significantly (r = 0:85; P<0:01) as PFOA contamination increased: log(BCF of PFOA) = -0.30 x log(PFOA level in river water) + 1.5.

Age, sex, and species and their interactions had no detectable influence on the BCFs of PFOA in the analysis of covariance.

Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented and is acceptable for assessment

29.12.2006 (446) (447)

Species Exposure : other: Food web of the bottlenose dolphin Tursiops truncates
period : at °C
Concentration :
Elimination :
Method : other
Year : 2006
GLP : no
Test substance : other TS

Method : Samples Collection:
PFOA was analyzed in different biotic and abiotic media sampled around Charleston Harbor and its tributaries (i.e., the Cooper, Ashley, and Wando rivers) and the Stono River estuary, South Carolina, and in Sarasota Bay, Florida.
Marine water, surface sediment, Atlantic croaker (Micropogonias undulatus), pinfish (Lagodon rhomboides), red drum (Sciaenops ocellatus), spotfish (Leiostomus xanthurus), spotted seatrout (Cynoscion nebulosus), striped mullet (Mugil cephalus), and bottlenose dolphin samples were collected around the Charleston Harbor area.
Marine water, surface sediment, zooplankton, sheephead (Archosargus

probatocephalus), pigfish (Orthopristis chrysoptera), pinfish, striped mullet, spotted seatrout, and bottlenose dolphin samples were collected at Sarasota Bay.

Seawater samples were collected at both locations in 2004 using 4 L polypropylene (PP) bottles. The bottles were submerged in 0.2-0.5 m of water, uncapped and filled, then recapped underwater. Water samples were kept at 4°C until analysis.

Surface sediment samples were collected in 2004 throughout Sarasota Bay (n = 8) and Charleston Harbor and surrounding waters (n=17). Sediment samples were collected using a Ponar grab sampler in Sarasota and a Young (modified vanVeen) grab sampler in Charleston. Samples were then transferred into PP jars for storage at 4°C.

Twenty-four hour composites (samples collected every hour and then pooled) of wastewater treatment plant effluent (WWTP) were collected in PP bottles at four different facilities in the Charleston area.

Zooplankton samples were collected by trawling in Sarasota Bay (2004) using a 100 µm mesh-size net, transferred into a 50 ml PP tube, and kept at -20°C. The freezing of samples prevented the identification of zooplankton species.

Fish were captured in 2002-03 at Charleston by trammel net and 2004 at Sarasota Bay by purse seine. Fish were weighed, measured, homogenized, and stored at -20°C in PP containers until analysis.

Dolphin plasma, skin, and teeth were collected from both locations during capture-release events that took place in the summer of 2004. Additionally, dolphin tissue samples (i.e., liver, kidney, muscle, lungs, heart, thyroid, and thymus) were collected in PP bags or vials during the necropsies of recently deceased bottlenose dolphins from Sarasota Bay (2002, n=1, male, 233.5 kg) and Charleston (2003, n=1, female, 708.4 kg). Additional liver (n=6) and kidney (n=6) samples collected from stranded bottlenose dolphins were available at Sarasota Bay. Dolphin tissue samples were kept at -20°C until analysis.

Chemical analysis:
Concentrations of PFCs in samples were determined by high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/ MS). HPLC-MS/MS detection utilized a negative ion turboelectrospray API2000 (Applied biosystems-MDS Sciex) for fish and plasma of dolphin. Analyses of water, sediment, and zooplankton were conducted with a negative ion turboelectrospray API4000 using an Agilent pump with the Teflon parts removed in order to improve detection limits of PFOA.

Remark : The authors calculated biomagnification factors for several predators and their prey, but it is difficult to understand how they calculated these factors. For example: At Charleston, for seatrout/pinfish a BMF of 7.2 is reported. However, a recalculation from data given in the report, indicates seatrout residues (1.8 ng/g) divided by pinfish residues (<0.5 ng/g) should be 3.6. The BMFs for dolphins and their prey can not be recalculated because they are based on whole body concentration in dolphins. The extrapolation factors from plasma and tissue to whole body is not transparent. In addition the water and biota samples were originating from different years with high variabilities. Keeping these uncertainties in mind, the maximum BMF for dolphin (whole)/striped mullet (whole) and dolphin(whole)/pinfish(whole) was 13.

Result : Arithmetic mean concentrations ± standard deviation (ng/l for seawater, WWTP; ng/g wet weight for sediment, whole zooplankton, whole fish and plasma of dolphins) of PFOA:

	Charleston	Sarasota Bay
water	9.5 ± 13	3.6 ± 9.2
sediment	0.2 ± 0.2	0.06 ± 0.02
WWTP	59 ± 26	--*
zooplankton	--*	0.3 ± 0.5
striped mullet	<0.5 #	<0.5 #
pigfish	<0.5 #	<0.5 #
red drum	1.2 ± 1.4 1.4	--*
Atl. croaker	± 1.6 0.5 ±	--*
spotfish	0.3 1.8 ± 3.2	--*
spotted seatrout	43 ± 24	<0.5 #
bottlenose dolphin		3.4 ± 3.5

* no samples collected at this location
# below limit of detection

The authors calculated the following biomagnification factors for several predators and their prey for Charleston:

predator/prey (BMFs)*

seatrout/pinfish = 7.2
dolphin/striped mullet = 13
dolphin/pinfish = 13
dolphin /red drum = 2.7
dolphin/Atlantic croaker = 2.3
dolphin/spotfish = 6.4
dolphin/seatrout = 1.8

* BMFs are based on PFOA measurements in whole fish and zooplankton homogenates and whole dolphin body burden estimations.

Test substance : PFOA
Reliability : (2) valid with restrictions
Study was well documented and is acceptable for assessment

08.12.2006 (328)

Species Exposure : other: Eastern Arctic food web
period : at °C
Concentration :
Elimination :
Method : other
Year : 2004
GLP : no
Test substance : other TS

Method : Sample collection:

Fluorinated organic compounds were analyzed in liver tissues of beluga whale (Delphinapterus leucas), narwhal (Monodon monoceros), walrus (Odobenus rosmarus), deepwater redfish (Sebastes mentella), glaucous gulls (Larus hyperboreus), and black-legged kittiwake (Rissa tridactyla). Whole organism homogenates of Arctic cod (Boreogadus saida), shrimp (Pandalus borealis; Hymenodora glacialis), clams (Mya truncata; Serripes groenlandica), and mixed zooplankton were analyzed.

Chemical analysis:

Analyses were performed with a Sciex API 2000 triple quadrupole mass spectrometer (MDSSciex, Ontario, Canada) in the negative ion ES mode using multiple reaction monitoring.

Method Detection Limit (MDL) of PFOA was estimated to be 0.2 ng/g.

Remark : Mammal samples were obtained through the Department of Fisheries and Oceans collection programs as part of subsistence hunts and sponsored by the Nunavut Wildlife Management Board. Seabirds were collected as part of the Northwater Polyna study. Archived mammal tissues were collected from Frobisher Bay near Iqaluit (beluga; 1996), from Cape Dorset (walrus; 1998), and from Grise Fiord (narwhal; 2000). Beluga (aged 3.5-10.5 yr) and narwhal were all males, while walrus samples consisted of both sexes. Fish and shrimp were collected from Davis Strait in October of 2000 and 2001 by trawling from the Greenland Institute of Natural Resources R/V Paamiut. Arctic cod were young of the year and 2 years of age, and deepwater redfish ranged in age from 4 to 7 yr. Clams and zooplankton samples were collected from Frobisher Bay in May 2002. Zooplankton samples consisted of bulk sieved mixed species (predominantly copepods with 5th stage Calanus hyperboreus removed) collected using 350 and 500 µm mesh nets. Clams were collected by a diver.

Result : Mean concentrations (arithmetic mean ± 1 SE, ng/g wet wt) of PFOA:

zooplankton = 2.6 ± 0.3 (n=5)
clams = nd* (n=5)
shrimp = 0.17 ± 0.05 (n=7)
Arctic cod = 0.16 ± 0.06 (n=6)
redfish = 1.2 ± 0.8 (n=7)
walrus = 0.34 ± 0.09 (n=5)
narwhal = 0.9 ± 0.1 (n=5)
beluga = 1.6 ± 0.3 (n=5)
black-legged kittiwake = nd*
glaucous gulls = 0.14 ± 0.05 (n=5)

* below MDL

PFOA was detected in 3 of the 7 shrimp samples, 1 of 6 Arctic cod samples, and in 2 of 7 redfish samples.

Statistical differences in the mean PFOA concentrations were observed between walrus (0.34 ± 0.09 ng/g) and narwhal (0.9 ± 0.1 ng/g; $p < 0.005$) and between walrus and beluga (1.6 ± 0.3 ng/g; $p < 0.05$). Biomagnification of PFOA between individual feeding relationships can be seen but not through the entire food web:

predator/prey (BMFs)

walrus/clam = 1.8
narwhal/arctic cod = 1.6
beluga whale/arctic cod = 2.7
beluga whale/redfish = 0.8
black-legged kittiwake/arctic cod = 0.3
glaucous gullus/arctic cod = 0.6
arctic cod/zooplankton = 0.04

Test substance : PFOA

Reliability : (2) valid with restrictions
Study was well documented and is acceptable for assessment

08.12.2006 (599)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	800
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

The acute toxicity of APFO to unfed fingerling rainbow trout, Oncorhynchus mykiss, was determined in an unaerated, 96-hour, static test in accordance with the Organisation for Economic Co-Operation and Development (OECD) Guideline for Testing Chemicals: 203; the European Economic Community 92/69 Annex V - Method C.I; and the United States Environmental Protection Agency, Pesticide Assessment Guidelines Subdivision E, 72-1.

The study was conducted with 5 nominal concentrations (625, 1250, 2500, 5000, and 10,000 mg/L) of APFO and a dilution water control at a mean temperature of 11.8°C (range of 11.6-12.1°C). Test solutions were not renewed during the 96-hour exposure. Two replicate test chambers were used per test concentration with 10 fish in each chamber (20 fish per concentration). Fish in the water control averaged 2.8 cm in standard length and 0.21 g in wet weight, blotted dry, at test end.

Concentrations were measured directly by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). All scheduled samples were analyzed on the day of receipt. The Day 1 samples were stored refrigerated till Day 4. The Day 1 samples were analyzed on Day 4 together with the Day 4 samples.

Test conditions:
Dilution water: Haskell Laboratory well, hardness of the well water is adjusted to approximately 110-140 mg/L as $CaCO_3$, aerated, passed through a green sand filter to remove iron, and filtered to remove particulates.

Result :

Exposure of rainbow trout to mean, measured concentrations of 554, 1090, 2280, 4560, and 9360 mg/L (nominal concentrations were 625, 1250, 2500, 5000, and 10,000 mg/L, respectively) resulted in 0, 0, 0, 75, and 100% mortality, respectively, at the end of 96 hours. No mortality was observed in the control. Surviving fish exposed to 4560 mg/L exhibited effects such as swimming at the surface, labored respiration, dark coloration, lethargy, and erratic swimming. There were no mortality or sublethal effects below 4560 mg/L.

Dilution water chemistry:
pH range: 7.1-7.2
Total alkalinity: 49 mg/L (as $CaCO_3$)
EDTA Hardness: 122 mg/L (as $CaCO_3$)
Dissolved oxygen range: 7.5-11.1 mg/L
Temperature range: 11.6-12.1°C

Test substance	:	20% APFO in water
Reliability	:	(1) valid without restriction Well documented test report, meets validity criteria of the test guideline

Flag : Critical study for SIDS endpoint
07.12.2006 (204)

Type : static
Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 125
LC50 : 707
Limit test :
Analytical monitoring : no
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The acute toxicity of the test item APFO was evaluated in the rainbow trout, Oncorhynchus mykiss, using a 96-hour static test according to OECD Guideline (No. 203, 17th July 1992) and Commission Directive 92/69/EEC (C.1, 31st July 1992). The criterion measured is the LC50 (Median Lethal Concentration), a statistically derived concentration of the test item which is expected to cause death in 50% of the animals. The test item was dissolved in water (total hardness between 150 ± 20 mg/L as CaCO3).

Six groups of seven fish were exposed to nominal concentrations of 31.3, 62.5, 125, 250, 500, and 1000 mg/L expressed as the APFO (solids) content of the test item for 96 hours while a further group of seven fish was exposed to test dilution water only (control solution).

No analysis was carried out to confirm the test concentrations based on information from the sponsor that the test item was stable in water, which has been subsequently confirmed experimentally.

Test conditions:
Dilution water: Water was filtered, dechlorinated, softened, and deionized

Result : Mortality was 0% at 31.3, 62.5, 125, 250 and 500 mg/L after 96 hours; mortality was 100% at 1000 mg/L after 24 hours. No mortality was observed in the control.

Sub-lethal effects were observed at 250 and 500 mg/L. They corresponded to animals lying at the bottom of the aquarium, color change and abnormal respiratory rate at 250 mg/L and to color change and abnormal respiratory rate at 500 mg/L. For both concentrations, this abnormal respiratory rate was observed from 24 to 72 hours but not subsequently.

Dilution water chemistry:
pH range: 7.32-7.88
Temperature: 14.7-15.4°C
Dissolved oxygen: 6.0-10.0 mg/L
Water hardness: 162-164 mg/L (as CaCO3)

Test substance : 19.6% APFO in water
Reliability : (1) valid without restriction
Well documented test report, meets validity criteria of the test guideline

Flag : Critical study for SIDS endpoint
07.12.2006 (122)

Type : static
Species Exposure : Lepomis macrochirus (Fish, fresh water)
period : 96 hour(s)
Unit : mg/l
LC50 : 634
Limit test :

Analytical monitoring : no
Method : EPA OTS 797.1400
Year : 1994
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The toxicity of APFO was determined in a static, acute 96-hour LC50 study in bluegill sunfish, Lepomis macrochirus. The test item was dissolved in water. Seven groups of 10 fish were exposed to nominal concentrations of 262, 328, 410, 512, 640, 800, and 1000 mg/L expressed as the APFO (solids) content of the test item for 96 hours while a further group of 10 fish was exposed to test dilution water only (control solution).

Test conditions:
Dilution water: Haskell Laboratory well water

Result : A range-finder was conducted. Nominal test concentrations were 0, 0.1, 1, 10, 100, and 1000 mg/L. Mortality after 96 hours was 0, 0, 0, 0, 0, and 80%, respectively.

The definitive study was conducted using nominal concentrations of 0, 262, 328, 410, 512, 640, 800, and 1000 mg/L. Mortality after 96 hours was 0, 5, 10, 15, 30, 40, 65, and 95%, respectively.

Surviving fish appeared lethargic at 800 and 1000 mg/L. No adverse effects were seen at lower concentrations.

Dilution water chemistry:
Temperature range: 21.3-22.1°C
Dissolved oxygen range: 6.7-8.5 mg/L
pH range: 6.9-7.5
Total alkalinity: 79 mg/L (as $CaCO_3$)
EDTA Hardness: 76 mg/L (as $CaCO_3$)

Reliability : (2) valid with restrictions
Stability and solubility of the test substance under test and storage conditions were not determined and endpoints are based on nominal test concentrations.

13.01.2006 (199)

Type : static
Species : Lepomis macrochirus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : > 420
Limit test :
Analytical monitoring : no
Method : other
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 20 bluegill sunfish were exposed for 96 hours to nominal concentrations including 0 (control), 135, 180, 240, 320, or 420 mg/L of APFO dissolved in water.

Test conditions:
Dilution water: Carbon-filtered well water

Result : Dilution water chemistry:

Temperature: 19°C
Dissolved oxygen: 9.1 ppm
pH: 7.9

Reliability : (3) invalid

Testing lacks information on the method followed. No information on stock or test solution preparations. Average fish weight is suspect. Sample purity was not characterized and the study lacks analytical confirmation of test substance concentrations.

13.01.2006 (29)

Type : static
Species : Lepomis macrochirus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 569
Limit test :
Analytical monitoring : no
Method : other
Year : 1978
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 20 bluegill sunfish were exposed for 96 hours to nominal concentrations of 0 (control), 420, 560, 750, 1000, or 1350 mg/L of APFO dissolved in water (carbon-filtered well water).

Result : In the groups of 20 fish exposed to nominal concentrations of 0 (control), 420, 560, 750, 1000, or 1350 mg/L, mortality at 96 hours was 5, 20, 50, 70, 100, and 100%, respectively.

Dilution water chemistry:

Temperature: 19°C
Dissolved oxygen: 9.9 ppm
pH: 7.6

Reliability : (3) invalid
Testing lacks information on the method followed. No information on stock or test solution preparations. Sample purity was not properly characterized and the study lacks analytical confirmation of test substance concentrations.

13.01.2006 (30)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 766
Limit test :
Analytical monitoring : no
Method : other: EPA 660/3-75-009
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 20 fathead minnows were exposed for 96 hours to nominal concentrations of 0 (control), 560, 650, 750, 870, or 1000 mg/L of APFO dissolved in water (carbon-filtered well water).

Result : Specific mortality data were not available. The reported 96-hour LC50 of 766 mg/L is the average of the values obtained in 2 replicates (776 and 754 mg/L, respectively).

Dilution water chemistry:

pH: 7.9-8.0
Temperature range: 18-19°C
Dissolved oxygen range: 4.0-5.9 mg/L (45-56% oxygen saturation)

Reliability : (2) valid with restrictions

Testing meets the criteria for testing at the time it was conducted.
However, sample purity was not properly characterized and the study lacks analytical confirmation of the test substance concentrations.

07.12.2006 (34)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : > 1000
Limit test :
Analytical monitoring : no
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 10 fathead minnows were exposed for 96 hours to 0 (control), 150, 250, 400, 600, and 1000 mg/L nominal concentrations of APFO dissolved in well water.
Remark : No mortality was seen in the control and up to the highest concentration tested (1000 mg/L of a 45% APFO solution). Therefore the LC50 concentration is greater than 450 mg/L of APFO.
Result : Dilution water chemistry:

pH: 7.4
Dissolved oxygen range: 6.1-9.2 mg/L
Conductivity: 1500 umhos/cm
Hardness: 88 mg/L (as CaCO3)
Temperature: 21-22°C (1000 mg/L exposure)

Test substance : Less than 45% APFO in water
Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. However, sample purity was not properly characterized and the study lacks analytical confirmation of test substance concentrations.

07.12.2006 (253)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 301
Limit test :
Analytical monitoring : no
Method : other
Year : 1987
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 6 fathead minnows were exposed for 96 hours to 0 (control), 100, 180, 320, 560, and 1000 mg/L nominal concentrations of APFO dissolved in water (carbon-filtered well water).
Result : Mortality at 96 hours for the 0 (control), 100, 180, 320, 560, and 1000 mg/L groups was 0, 0, 13, 50, 100, and 100%, respectively.

Dilution water chemistry (initial):

Temperature: 20°C
Dissolved oxygen range: 6.6-7.4 mg/L in control
5.6-6.6 mg/L at 320 mg/L
pH: 7.7-8.0

Test substance : APFO; purity greater than 78%

Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. However, sample purity was not properly characterized and the study lacks analytical confirmation of test substance concentrations.

07.12.2006 (44)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 2470
Limit test :
Analytical monitoring : no
Method : EPA OTS 797.1400
Year : 1996
GLP : no
Test substance : other TS

Method : Groups of 20 fathead minnows were exposed for 96 hours to nominal concentrations of 0 (control), 530, 830, 1330, 2100, and 3330 mg/L of APFO dissolved in water.

Remark : The 96-hour LC50 of 2470 mg/L is based on the test sample which was 20% APFO. Therefore, the 96-hour LC50 based on APFO would be 494 mg/L.

Result : Mortality in the 0, 530, 830, 1330, 2100, and 3330 mg/L groups at 96 hours was 0, 0, 0, 5%, 15%, and 100%, respectively. The only fish that were affected were in the 3330 mg/L group where 6 of the 17 surviving fish exhibited lethargy and a loss of equilibrium after 24 hours of exposure.

Test conditions:

Hardness: 44 mg/L as CaCO3
Alkalinity: 29-30 mg/L as CaCO3
pH Range (0-96 hours): 7.2-7.7 (at 2100 mg/L)
Temperature range (0-96 hours): 21.8-22.5°C (at 2100 mg/L)
Dissolved oxygen range (0-96 hours): 5.7-9.2 mg/L (at 2100 mg/L)

Test substance : 20% APFO in water. The purity was not sufficiently characterized, though current information indicates this sample was a 30% straight carbon version of APFO.

Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. However, sample purity was not properly characterized and the study lacks analytical confirmation of test substance concentrations.

07.12.2006 (583)

Type : static
Species : Lepomis gibbosus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : 1550
Limit test :
Analytical monitoring : no
Method : other
Year : 1966
GLP : no
Test substance : other TS

Method : Groups of 10 pumpkinseed sunfish were exposed for 48 hours to 0 (control), 100, 1000, 2400, or 10,000 mg/L (nominal) of the test material.

Result : Test conditions:

Temperature: 20°C

Dissolved oxygen: 5 to 9 ppm
pH: 6.8

Test substance : APFO of unknown purity
Reliability : (3) invalid
No information is given on the method followed. Sample purity was not stated and no analytical confirmation of test substance concentrations was given.

13.01.2006 (161)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 110
LC50 : 140
Limit test :
Analytical monitoring : no
Method : EPA OTS 797.1400
Year : 1996
GLP : yes
Test substance : other TS

Method : Groups of 10 fathead minnows were exposed for 96 hours to 0 (control), 65, 110, 180, 300, and 500 mg/L nominal concentrations of PFOA dissolved in isopropanol.

Test conditions:
Dilution water: Deionized water adjusted to a hardness of 40-48 mg/L as CaCO3.

Result : Mortality at 96 hours was 0, 0, 0, 100, 100, and 100% at nominal concentrations of 0, 65, 110, 180, 300, and 500 mg/L, respectively.

The pH of the test solutions for the 180, 300, and 500 mg/L exposure concentrations were in the range of 3.0-4.3 at test initiation. This low pH would have adversely affected the survival of the fish.

Dilution water chemistry (220 mg/L exposure):
Temperature: 21.9-22.6°C
Dissolved oxygen range: 5.2-8.8 mg/L
pH range: 6.2-7.2

Test substance : PFOA (purity greater than 96.5%)
Reliability : (2) valid with restrictions
The study lacks analytical measurement of test substance concentrations. The low pH values in the high concentrations tested may have had an adverse affect on survival.

13.01.2006 (580)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 440
Limit test :
Analytical monitoring : no
Method : other
Year : 1974
GLP : no
Test substance : other TS

Method : Groups of fathead minnows (number not stated) were exposed for 96 hours to 0 (control), 50, 125, 250, 375, or 500 mg/L nominal concentrations of PFOA.

Result : Mortality at 96 hours in the (control), 50, 125, 250, 375, and 500 mg/L groups was 0, 0, 0, 0, 0, and 100%, respectively.

pH values were 7.2 in the control at 24, 48, 72, and 96 hours, 7.0 at each time point at 50 mg/L, range of 6.5 to 6.9 at 125 mg/L, 6.4 to 6.6 at 250 mg/L, and 6.0 to 6.4 at 375 mg/L. All the fish were dead by 48 hours at 500 mg/L. Dissolved oxygen ranges for 24-96 hours were 4.7-5.7 mg/L in controls and 3.8-5.2 mg/L in the 375 mg/L exposure group. Temperature range was 69-70°F (= 20.5-21°C)

Test substance : PFOA (greater than 96.5% purity)

Reliability : (2) valid with restrictions
This study lacks documentation and information on the methodology. Test concentrations were not characterized.

07.12.2006 (25)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 843
Limit test :
Analytical monitoring : no
Method : other
Year : 1985
GLP : no
Test substance : other TS

Method : Groups of 5 fathead minnows were exposed for 96 hours to 0 (control), 690, 750, 810, 870, or 930 mg/L nominal concentrations of PFOA in water (carbon-filtered well water).

Result : Mortality at 96 hours in the 0 (control), 690, 750, 810, 870, and 930 mg/L groups was 0, 0, 10, 30, 50, and 100%, respectively.

Dilution water chemistry at test initiation:
Temperature: 19°C
Dissolved oxygen: 9.5 ppm
pH: 7.8

Test substance : PFOA (purity greater than 95%)

Reliability : (3) invalid
The study lacks documentation on study methodology and lacks analytical confirmation of test substance concentrations.

13.01.2006 (39)

Type : static
Species Exposure : Pleuronectes platessa (Fish, marine)
period :
Unit :
Method : other
Year : 1997
GLP :
Test substance : other TS

Method : Juvenile and adult plaice were obtained by trawl off the Scottish east coast and kept in filtered recirculating seawater at a constant 10°C for 2 weeks before use. Animals were fed ad libitum during this period. beta-Naphthoflavone (BNF) and perfluorooctanoic acid (PFOA) were both administered to male fish only by a single intraperitoneal injection at 50 mg per kg 72 h prior to analysis. The fish were not fed during this period. This BNF dose is typical of that used to induce cytochrome P-4501A in fish species, while the PFOA dose used is one-quarter of the 30-day LD50 in the rat for a single intraperitoneal injection.

Result : Glutathione S-transferases are involved in the detoxification of reactive

electrophilic compounds, including intracellular metabolites, drugs, pollutants and pesticides. A cluster of three glutathione S-transferase genes, designated GSTA, GSTA1 and GSTA2, was isolated from the marine flatfish, plaice (Pleuronectes platessa). GSTA and GSTA1 code for protein products with 76% amino acid identity. GSTA2 appears to contain a single nucleotide deletion which would render any product non-functional. All of these genes consist of six exons of similar sizes and greater than 70% nucleotide identity, and are interrupted by five introns of differing sizes. GSTA and GSTA1 mRNAs were present in a range of tissues, while GSTA2 mRNA was no detected. Expression of GSTA mRNA was increased in plaice intestine and spleen by pretreatment with beta-naphthoflavone, and expression of both GSTA and GSTA1 mRNAs was increased in plaice liver and gill by pretreatment with the peroxisome proliferating agent perfluorooctanoic acid.

Test substance : PFOA
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

13.01.2006 (406)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 480
Analytical monitoring : no
Method : Directive 92/69/EEC, C.2
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Five groups of 20 daphnids (in four replicates of five) were subjected to nominal test item concentrations of 100, 178, 316, 562 and 1000 mg/L expressed as the APFO (solids) content of the test item for a period of 48 hours while a second group of 20 daphnids (in four replicates of five) was exposed to test water (M4) only (control solution).

Result : After 48 hours, immobilizations were 0% at 0, 100, 178 and 316 mg/L, 80% at 562 mg/L and 100% at 1000 mg/L.

Test conditions:

Dilution water: Reconstituted (M4). The pH of this solution is 8.0; the sum of Ca and Mg ions in the solution is 2.5 mmol/L (molar ratio Ca:Mg is approximately 4:1 and Na:K approximately 10:1); total hardness is generally between 238 and 289 mg/L as $CaCO_3$.

Dilution water chemistry:
pH range: 7.64-8.17
Hardness: 289 mg/L (as $CaCO_3$)
Temperature range: 19.6-20.3°C
Dissolved oxygen range: 8.2-8.5 mg/L

Test substance : 19.6% APFO solution in water.
Reliability : (1) valid without restriction
Well documented test report, testing meets the validity criteria for quality testing. While analytical confirmation of test substance concentrations was not conducted, the test substance is expected to be stable under the conditions of the test.
Flag : Critical study for SIDS endpoint

07.12.2006 (120)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 221
Analytical monitoring : no
Method : other
Year : 1987
GLP : no
Test substance : other TS

Method : Groups of 10 daphnids were exposed for 48 hours to nominal APFO concentrations of 0 (control), 100, 180, 320, 560, or 1000 mg/L in well water.

Result : In groups of 10 daphnids exposed for 48 hours to nominal APFO concentrations of 0 (control), 100, 180, 320, 560, or 1000 mg/L in well water, percent mortality was 0, 0, 40%, 80%, 100%, and 100%, respectively in the first trial and 0, 0, 40%, 70%, 100%, and 100%, respectively, in a second trial. Overall, the 48-hour EC50 was 221 mg/L.

Dilution water chemistry:

pH: 7.9
Temperature: 21°C
Dissolved oxygen: 9.4 mg/L

Test substance : APFO (greater than 78% purity).

Reliability : (3) invalid
Test methodology was not given and the study lacks analytical confirmation of test substance concentrations.

13.01.2006 (43)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 584
Analytical monitoring : no
Method : OECD Guide-line 202
Year : 1990
GLP : yes
Test substance : other TS

Method : Groups of 5 daphnids were exposed for 48 hours to 0 (control), 150, 250, 400, 600, or 1000 mg/L nominal concentrations of APFO. There were 4 replicates of each test (total of 20 daphnids per group).

Remark : The EC50 value listed is based on the 50% APFO test solution. Therefore the value expressed as 100% APFO would be 292 mg/L.

Result : Most of the exposed daphnids survived the 48-hour exposure. Mortality was seen in only the 600 (10%) and 1000 mg/L (25%) groups. Daphnids were immobilized only in the 600 (90%) and 1000 mg/L (100%) groups. No mortality was observed in the control. The 48-hour EC50 was 584 mg/L of a 50% APFO solution.

Dilution water chemistry:

pH range: 8.1-8.4
Hardness: 180 mg/L (as $CaCO_3$)
Temperature range: 19.5-20.1°C (1000 mg/L exposure)
Dissolved oxygen range: 9.1-9.5 mg/L (1000 mg/L exposure)

Test substance : 50% water solution of APFO (purity less than 45%).

Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (252)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : 730
EC50 : 1200
LC50 : 1550
Analytical monitoring : no
Method : EPA OTS 797.1300
Year : 1996
GLP : yes
Test substance : other TS

Method : Groups of 10 daphnids were exposed for 48 hours to nominal APFO concentrations of 0 (control), 430, 730, 1200, 2000, and 3330 mg/L in water.

Test conditions:
Dilution water: Deionized water adjusted to a hardness of 160-180 mg/L (as CaCO3)

Remark : The NOEC, EC50, and LC50 values listed are based on the 20% APFO test solution. Therefore the values expressed as 100% APFO would be 146, 240, and 310 mg/L, respectively.

Result : There were 2 replicates of this test (total of 20 daphnids per test concentration). In the groups of 10 daphnids exposed for 48 hours to nominal APFO concentrations of 0 (control), 430, 730, 1200, 2000, and 3330 mg/L in water, percent mortality was 0, 0, 0, 5, 95, and 100%, respectively. Immobilization in the surviving dapnids was 0, 0, 0, 47, and 100% in the 0 (control), 430, 730, 1200, and 2000 mg/L groups, respectively. All the daphnids exposed at 3330 mg/L were dead.

Dilution water chemistry:

pH range: 8.1-8.2 (2000 mg/L exposure)
Hardness: 176 mg/L (as CaCO3)
Temperature range: 20.3-20.8°C (2000 mg/L exposure)
Dissolved oxygen range: 8.1-9.1 mg/L (2000 mg/L exposure)

Test substance : 20% APFO solution in water: purity is not sufficiently characterized.
Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. Nominal test conditions.

13.01.2006 (582)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : 180
EC50 : 360
48-hour LC50 : 400
24-hour LC50 : 500
Analytical monitoring : no
Method : EPA OTS 797.1300
Year : 1996
GLP : yes
Test substance : other TS

Method : Groups of 10 daphnids were exposed for 48 hours to nominal PFOA concentrations of 0 (control), 130, 200, 360, 600, or 1000 mg/L (tested as a

50:50 mixture of test material and isopropanol). The concentration of test material in solution was 65, 110, 180, 300, and 500 mg/L.

Result : There were 2 replicates of each concentration (for a total of 20 daphnids for each test concentration). In the groups of 10 daphnids exposed for 24 or 48 hours to nominal PFOA concentrations of 0 (control), 65, 100, 180, 300, and 500 mg/L in water, percent mortality was 0, 0, 0, 0, 10, and 50%, respectively, at 24 hours and 0, 0, 0, 0, 15, and 80%, respectively, at 48 hours. Immobilization in the surviving daphnids was 0, 0, 0, 0, 0, and 80%, respectively.

Dilution water chemistry:

pH range: 7.5-8.0 (1000 mg/L exposure)
Temperature range: 19.4-20.2°C (1000 mg/L exposure)
Dissolved oxygen range: 8.7-8.8 mg/L (1000 mg/L exposure)

Test substance : PFOA (purity greater than 96.5%).

Reliability : (2) valid with restrictions
The study lacks analytical measurement of test substance concentrations in the test solutions.

13.01.2006 (584)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 126
Analytical monitoring : no
Method : other
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 10 daphnids were exposed for 48 hours to nominal APFO concentrations of 0 (control), 10, 30, 100, 300, and 1000 mg/L.

Result : Dilution water chemistry:

pH: Not listed in report
Hardness: Not listed in report
Temperature range: 24°C
Dissolved oxygen range: Not listed in report

Reliability : (3) invalid
The method is not described, sample purity was not properly characterized, and the study lacks analytical measurement of test substance concentrations. The values from multiple tests contradict each other. The purpose of these studies was to evaluate different daphnid diets.

13.01.2006 (36)

Type : static
Species : other aquatic crustacea: snail
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : 246
48-hour LC50 : 820
Analytical monitoring : no
Method : other
Year : 1966
GLP : no
Test substance : other TS

Method : Groups of 10 snails were exposed for 48 hours to nominal APFO concentrations of 0 (control), 560, 1000, 1550, and 3100 mg/L in synthetic Ohio River water.

Result : Dilution water chemistry:

Temperature: 20°C
Dissolved oxygen: 5 to 9 ppm
pH: 6.8
Total hardness: 204 ppm (as $CaCO_3$)

Test substance : APFO of unknown purity

Reliability : (3) invalid
No information is given on the method followed. Sample purity was not stated and no analytical confirmation of test substance concentrations was given.

13.01.2006 (161)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae: Pseudokirchneriella subcapitata
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 12.5
EC50 : > 400
Limit test :
Analytical monitoring : yes
Method : Directive 92/69/EEC, C.3
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this study was to assess the acute toxicity of APFO, to Pseudokirchneriella subcapitata (previously named Selenastrum capricornutum), in a 96-hour static test. The criterion measured is the EC50 (Median Effective Concentration), a statistically derived concentration of the test item in water which can be expected to cause a reduction of algal growth of 50% in comparison with the control.

One range-finding test and two tests with the same test concentrations and test conditions were conducted.

Range finding test: 0.01; 0.1; 1; 10 and 100 mg/L

First and second test: For the stock solutions an amount of 2041 mg test item as received (= 400 mg APFO solids) was added directly to reconstituted water. Afterwards the stock solutions were agitated for 15 minutes. Agitation was continued until the stock solutions were used to prepare the test solutions.

Nominal concentrations: 0, 5.25, 12.5, 25, 50, 100, 200, 400 mg/L (expressed as APFO (solids) contents)

Analyses were conducted for each test concentration after 0 and 96h. An aliquot of each sample (test water with and without algae) was diluted and analyzed by Ion Chromatography with Electrochemical Detection (Conductimetry). Concentrations were within 85 to 102% in all test vessels. For this reason all results are based on nominal concentrations.

Test conditions:

Dilution water: The test item was dissolved in reconstituted water with a hardness of approximately 34 mg/L as $CaCO_3$; Temperature was 22.6°C to 23.8°C; Continuous illumination; pH: between 6 and 9 after preparation, no

adjustment of pH before adding of the algae.

Result : Range-Finding Test

Conc.
[mg/L] Inhib. growth rate Inhib. biomass

	72h	96h	72h	96h
0.01	0 %	0 %	0 %	0 %
0.1	0 %	2 %	1 %	4 % 5
1.0	0 %	1 %	10 %	%
10	0 %	1 %	8 %	4 %
100	4 %	1 %	31 %	17 %

First Test

Variation coefficient of control cell density at 72h: 10.2% and 96h: 7.73%.:

Conc.
[mg/L] Cell number (x10E4) after

	0h	24h	48h	72 h	96h
0	1.0	4.2	35	199	433
6.25	1.0	4.2	40	236	402
12.5	1.0	4.2	39.8	233	369
25.0	1.0	4.0	41.2	224	351
50.0	1.0	3.5	37.1	248	333
100	1.0	4.7	40	230	341
200	1.0	3.5	39.9	215	272
400	1.0	2.4	38.4	162	182

Results expressed as mean values of 6 replicates in control and 3 replicates in test concentrations:

Growth rate: 72h-ErC50 > 400 mg/L
72h-NOEC = 200 mg/L
96h-NOEC = 6.25 mg/L
96h-ErC50 > 400 mg/L

Biomass: 72h-EbC50 > 400 mg/L
72h-NOEC = 400 mg/L 96h-
ErC50 > 400 mg/L 96h-
NOEC = 100 mg/L

The large difference between growth rate NOECs (72h and 96h) and between growth rate and biomass NOECs at 96h in the first test were considered unusual. It was considered that the low slope of the concentration-effect curve may have prevented determination of precise
NOECs. The results were not considered conclusive and, consequently, a second test was performed to determine whether the results of the first test were reproducible, using the same range of concentration.

Second Test

Variation coefficient of control cell density at 72h: 11.3% and 96h: 8.0%

Conc.
[mg/L] Cell number (x10E4) after

	0h	24h	48h	72 h	96h
0	1.0	7.0	37	129	473

6.25	1.0	6.8	36	130	458
12.5	1.0	6.5	33.5	145	425
25.0	1.0	6.4	31.5	142	338
50.0	1.0	6.4	38	133	338
100	1.0	5.4	31	167	313
200	1.0	6.2	33	120	213
400	1.0	4.4	28	107	190

Results expressed as mean values of 6 replicates in control and 3 replicates in test concentrations.

Growth rate: 72h-ErC50 > 400 mg/L
72h-NOEC = 200 mg/L
96h-ErC50 > 400 mg/L 96h-NOEC = 12.5 mg/L

Biomass: 72h-EbC50 > 400 mg/L
72h-NOEC = 200 mg/L 96h-ErC50 > 400 mg/L 96h-NOEC = 12.5 mg/L

Test substance : 19.6% solution in water of APFO
Reliability : (1) valid without restriction
Well documented test report, meets validity criteria of the test guideline
Flag : Critical study for SIDS endpoint
07.12.2006 (124)

Species : other algae: Pseudokirchneriella subcapitata
Endpoint : biomass
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 12.5
EC50 : > 400
Limit test :
Analytical monitoring : yes
Method : Directive 92/69/EEC, C.3
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this study was to assess the acute toxicity of APFO, to Pseudokirchneriella subcapitata (previously named Selenastrum capricornutum), in a 96-hour static test. The criterion measured is the EC50 (Median Effective Concentration), a statistically derived concentration of the test item in water which can be expected to cause a 50% reduction of the biomass in comparison with the control.

Nominal concentrations of APFO were 0 (control), 6.25, 12.5, 25, 50, 100, 200, and 400 mg/L.

Test conditions:

Dilution water: The test item was dissolved in reconstituted water with a hardness of approximately 34 mg/L as $CaCO_3$.
Result : Dilution water chemistry:

pH range: 7.3 (t=0h) to 10.74 (t=96h)
Temperature range: 22.6°C to 23.8°C
Test substance : 19.6% solution in water of APFO
Reliability : (1) valid without restriction
Well documented test report, meets validity criteria of the test guideline
Flag : Critical study for SIDS endpoint
07.12.2006 (124)

Species : Selenastrum capricornutum (Algae)
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 430
EC50 : > 3330
24-hour EC50 : 1700
48-hour EC50 : > 3330
72-hour EC50 : > 3330
Limit test :
Analytical monitoring : no
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of the study was to determine the 24-, 48-, 72-, and 96-hour effective concentrations (EC) for growth rate and the number of cells/mL and the NOEC of the test substance to the freshwater alga, Selenastrum capricornutum under static conditions.

Nominal concentrations were 0 (control), 210, 430, 830, 1670, and 3330 mg/L.

3 Replicates per concentration (and control) were used.

Test conditions:

Dilution water: Sterile, enriched media adjusted to a target pH of 7.5 prior to use

Remark : The NOEC, 24-, 48-, 72-, and 96-hour EC50 values [430, 1700, > 3330, > 3330, and > 3330 mg/L] are based on the 20% APFO test solution. The values based on 100% APFO are 86, 340, > 666, > 666, and > 666 mg/L, respectively.

Result : Conc.
[mg/L] Cell number (x10E3) after

	0h	24h	48h	72 h	96h
0	10	33	136	674	1480
210	10	31	148	695	1468
430	10	33	142	627	1357
830	10	28	150	436	1168
1670	10	16	138	380	870
3330	10	14	84	254	467

Dilution water chemistry:

pH range: 7.4-7.6 (3330 mg/L exposure)
Temperature range: 24.0-24.2°C (incubator)

Test substance : 20% solution in water of APFO
Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. However, the study lacks information on the actual measurements of the amount of test substance in solution.

07.12.2006 (581)

Species : Selenastrum capricornutum (Algae)
Endpoint : other: Cell count
Exposure period : 96 hour(s)
Unit : mg/l

NOEC : 210
EC50 : 1980
24-hour EC50 : 2510
48-hour EC50 : > 3330
72-hour EC50 : 2040
Limit test :
Analytical monitoring : no
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of the study was to determine the 24-, 48-, 72-, and 96-hour effective concentrations (EC) for growth rate and the number of cells/mL and the no-observed-effect-concentration (NOEC) of the test substance to the freshwater alga, Selenastrum capricornutum, under static conditions.

The nominal concentrations were 0 (control), 210, 430, 830, 1670, and 3330 mg/L.

3 Replicates per concentration (and control) were used.

Test conditions:

Dilution water: Sterile, enriched media adjusted to a target pH of 7.5 prior to use

Remark : The NOEC, 24-, 48-, 72-, and 96-hour EC50 values [210, 2510, > 3330, 2040, and 1980 mg/L] are based on the 20% APFO test solution. The values based on 100% APFO are 42, 502, > 666, 408, and 396 mg/L, respectively.

Result : Conc.
[mg/L] Cell number (x10E3) after

	0h	24h	48h	72 h	96h
0	10	33	136	674	1480
210	10	31	148	695	1468
430	10	33	142	627	1357
830	10	28	150	436	1168
1670	10	16	138	380	870
3330	10	14	84	254	467

Dilution water chemistry:

pH range: 7.4-7.6 (3330 mg/L exposure)
Temperature range: 24.0-24.2°C (incubator)

Test substance : 20% water solution of APFO
Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. The study lacks actual measurements of the test solutions.

07.12.2006 (581)

Species : Selenastrum capricornutum (Algae)
Endpoint : other: Growth rate and cell density
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 63
EC50 : 90
72-hour EC50 : 90
Limit test :
Analytical monitoring : no
Method : EPA OTS 797.1050

Year : 1996
GLP : yes
Test substance : other TS

Method : The objective of the study was to determine the 24-, 48-, 72-, and 96-hour effective concentrations (EC) for growth rate and the number of cells/mL and the NOEC of the test substance to the freshwater alga, Selenastrum capricornutum under static conditions.

The nominal concentrations were 0 (control), 63, 125, 250, 500, and 1000 mg/L (tested as a 50:50 mixture of test substance and isopropanol). The nominal concentration of test substance in solution was 32, 63, 130, 250, and 500 mg/L.

Test conditions:
Dilution water: Sterile enriched media

Result : Conc.
[mg/L] Cell number (x10E3) after

	0h	24h	48h	72 h	96h	| pH range
0	10	21	168	360	1800	| 7.4-10.3
63	10	24	149	487	1732	| 6.8-10.3
125	10	21	109	513	1560	| 6.3-10.3
250	10	<10	<10	<10	<10	| 4.0-4.1
500	10	<10	<10	<10	<10	| 3.4-3.4
1000	10	<10	<10	<10	<10	| 2.9-3.0

The 96-hour EC50 for cell count is also 90 mg/l as is the 72-hour EC50 value. The 72-hour EC50 for growth rate is also 90 mg/l. The NOEC is 63 mg/L.

Dilution water chemistry:

Temperature: 23.5-24.0°C

Test substance : PFOA (purity greater than 96.5%)
Reliability : (2) valid with restrictions
The study lacks analytical measurement of test substance concentrations in the test solutions. Initial low pH values in the higher concentrations may have had an adverse effect on survival and growth of the algae.

07.12.2006 (585)

Species : Selenastrum capricornutum (Algae)
Endpoint : other: Cell count and dry weight
Exposure period : 96 hour(s)
Unit : mg/l
96-hour EC50 (cell count) : 49
96-hour EC50 (dry weight) : 149
Limit test :
Analytical monitoring : no
Method : other: Modified after EPA 600/9-78-018; ASTM-E-35.23, Draft No. 2; OECD
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : EC50 values were determined for algal cell counts (cells/mL) and cell dry weights by exposing the freshwater alga Selenastrum capricornutum for 4, 7, 10, and 14 days to nominal APFO concentrations of 0 (control), 100, 180, 320, 560, 1000, and 1800 mg/L.

Test conditions:
Dilution water: Sterile synthetic algal nutrient media

Result : Dilution water chemistry:

pH range: 7.4-7.6 (3330 mg/L exposure)
Temperature: 23°C (plus or minus 2°C)

Reliability : (4) not assignable
Basic data (like cell counts for t=0h to t=96h) not given in the report

07.12.2006 (35)

Species : Selenastrum capricornutum (Algae)
Endpoint : other: Cell count and dry weight
Exposure period : 14 day(s)
Unit : mg/l
EC50 (cell count) : 43
EC50 (dry weight) : 73
Limit test :
Analytical monitoring : no
Method : other: EPA 600/9-78-018 Draft No. 2
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : EC50 values were determined for algal cell counts (cells/mL) and cell dry weights by exposing the freshwater alga Selenastrum capricornutum for 4, 7, 10, and 14 days to nominal APFO concentrations of 0 (control), 100, 180, 320, 560, 1000, and 1800 mg/L.

Test conditions:
Dilution water: Sterile synthetic algal nutrient media

Result : Dilution water chemistry:

Temperature: 23°C (plus or minus 2°C)

Reliability : (3) invalid

08.12.2006 (35)

Species : other aquatic plant: Diatoms
Endpoint : growth rate
Exposure period : 168 hour(s)
Unit : mg/l
NOEC : 720
EC50 : 2400
Limit test :
Analytical monitoring : no
Method : other
Year : 1966
GLP : no
Test substance : other TS

Method : Diatoms were exposed for 7 days hours to nominal APFO concentrations of 0 (control), 1550, 2100, and 2800 mg/L in synthetic Ohio River Water.

After the 7-day test period, a count was made to determine the amount of growth that had occurred and this was compared to that of the untreated controls.

Result : Dilution water chemistry:

pH: 6.8
Temperature: 20°C
Dissolved oxygen range: 5-9 mg/L

Test substance : APFO of unknown purity

Reliability : (3) invalid
No information is given on the method followed. Sample purity was not stated and no analytical confirmation of test substance concentrations was given.

13.01.2006 (161)

Species : other aquatic plant: Myriophyllum sibiricum and Myriophyllum spicatum
Endpoint : other: Toxicity
Exposure period : 35 day(s)
Unit : mg/l
EC10 : >= 8.4
EC50 : >= 31.8
Limit test :
Analytical monitoring : yes
Method : other
Year : 2005
GLP : no
Test substance : other TS

Method : 30 artifical ponds with a volume of app. 12 m3, a diameter of 3.9 m and a surface area of 11.95 m2 were used. The microcosms are below ground with the tops flush with the surface. Sediment trays filled with amended sediment were placed in the bottom of each microcosm covering app. 50% of the available surface area. Sediment trays contain 1:1:1 mixture of sand, loam and organic matter (mainly composted manure) constructed below grade to a depth of 1.2m. Galvanized steel panels lined with food-grade PVC. Each microcosm has is filled with water to a depth of 1m and is flush with ground level. Total carbon content of the sediment was 16.3%, with inorganic carbon comprising 2.4% and the organic fraction being 14.9%. Prior to initiation of the study the microcosms were circulated for two weeks from a well-fed irrigation pond. Specific water quality parameters were measured regulary over the 35-day study period. At each measurement event, the mean for each treatment was calculated. These means were then averaged for all measurements:
Dissolved oxygen: range 7.3-8.5 mg/L
max. daily water temperature: range 21.5-22 mg/L
min. daily water temperature: range 17.8-18.3mg/L
pH: range 8.3-8.7
alkalinity: range 131-133 mg CaCO3/L
hardness: range 217-218 mg CaCO3/L

Replicate microcosms (n = 3) were treated with 0.3, 1, 30, and 100 mg/L PFOA as the sodium salt, plus controls, and assessed at regular intervals over 35 days.

Result : The relative sensitivity of the two species to PFOA was similar.

No statistically significant differences or concentration-response trends were noted after 7 days of exposure to PFOA in both species.

14 to 35d-NOEC = 23.9 mg/L
14 to 35d-LOEC = 74.1 mg/L

Myriophyllum spicatum:

14 to 35d-EC10 = 5.7 mg/L
14 to 35d-EC50 = 31.8 mg/L

Myriophyllum sibiricum:

14 to 35d-EC10 = 8.4 mg/L
14 to 35d-EC50 = 35.8 mg/L

Test substance : PFOA, sodium salt (purity not specified)

Reliability : (2) valid with restrictions
The sample purity was not specified.

13.01.2006 (304)

Species : Dunaliella salina (Algae)
Endpoint Exposure : growth rate
period :
Unit :
Method : other
Year : 1996
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Dunaliella salina algae was exposed in vitro to C-8. The algae did not die, but also did not grow.
Reliability : (4) not assignable
Original reference not yet available

13.01.2006 (202)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : > 1000
Analytical monitoring : no
Method : OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year : 1987
GLP : no
Test substance : other TS

Method : Nominal concentrations were 0 (two blank controls), 100, 180, 320, 560, and 1000 mg/L.

Test conditions:

Dilution water: Aerated, distilled, deionized water
Result : Dilution water chemistry:

pH: 7.4 (initial) and 8.1 (final) of the 1000 mg/L test concentration and 7.8 (initial) and 8.0 (final) of the activated sludge mixed liquor

Test Temperature range: 20-21°C
Test substance : APFO (purity greater than 78%).
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.
Flag : Critical study for SIDS endpoint

08.12.2006 (40)

Type : aquatic
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : > 3320
Analytical monitoring : no
Method : OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year : 1996
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Nominal concentrations included 0 (2 blank controls), 420, 840, 1660, and 3320 mg/L.

Test organism source: Activated sludge mixed liquor collected from a municipal wastewater treatment plant in St. Paul, MN.

Remark : The 3-hour EC50 value of > 3320 mg/L is for the 20% APFO test solution. Based on 100% APFO, the EC50 value would be > 664 mg/L.

Result : Test Conditions:

Dilution water: Millipore Milli-Q water
Temperature: 19.1-22.1°C
Total suspended solids and pH on day of testing: 3.22 g/L (TSS in final 1.3 g/L) and initial pH 7.8 and final pH 7.9
Element Basis: Respiration inhibition as determined by oxygen consumption

Test substance : 20% solution of APFO in water

Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

Flag : Critical study for SIDS endpoint

08.12.2006 (52)

Type : aquatic
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : > 1000
Analytical monitoring : no
Method : OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year : 1990
GLP : no
Test substance : other TS

Method : Only one nominal concentration was tested (1000 mg/L along with a control).

Inoculum source: Mixed liquor activated sludge collected from a municipal wastewater treatment plant in St. Paul, MN

Remark : The 3-hour EC50 value of > 1000 mg/L is for the 50% APFO test solution. Based on 100% APFO, the EC50 value would be > 500 mg/L.

Result : Test Conditions:

pH of Activated Sludge Mixed Liquor: 6.7 (initial) and 7.1 (final)

pH of 1000 mg/L test concentration: 7.3 (initial)

Temperature: 20-21°C

Test substance : 50% solution in water of APFO (purity less than 45%).

Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.
The testing procedure was also not fully documented.

08.12.2006 (46)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 870
EC20 : 420
Analytical monitoring : no
Method : other: Beckman's Microtox Basic Procedure
Year : 1987

GLP : no
Test substance : other TS

Method : Nominal concentrations include 0 (control), 420, 560, 750, and 1000 mg/L.
Result : Test conditions:

Diluent: 2% NaCl Microbic's Reagent
Deionized water pH: 6.5
Analytical monitoring: Light loss
Test substance : APFO (purity greater than 78%)
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (41)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 730
Analytical monitoring : no
Method : other: Microbics Microtox Basic Procedure
Year : 1996
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Nominal concentrations include 0 (control), 125, 250, 500, and 1000 mg/L.
Result : Test conditions:

Diluent: Millipore Milli-Q water
Test temperature: Not noted
pH of test solution: 5.8-7.6
Element basis: Percent light loss
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (49)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : > 1000
Analytical monitoring : no
Method : other: Microbics Microtox Basic Procedure
Year : 1990
GLP : no
Test substance : other TS

Method : Nominal concentrations include 0 (control), 125, 250, 500, and 1000 mg/L.
Remark : The 30-minute EC50 value of > 1000 mg/L is for the 50% APFO test solution. Based on 100% APFO, the EC50 value would be > 500 mg/L.
Result : Test conditions:

Diluent: 2% NaCl Microbic's Reagent
Test temperature: Not noted
Analytical monitoring: Light loss
Test substance : 50% solution in water of APFO (purity less than 45%)
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (45)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)

Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 1950
Analytical monitoring : no
Method : other: Microbics Microtox Basic Procedure
Year : 1996
GLP : no
Test substance : other TS

Method : Nominal concentrations include 0 (control), 416, 832, 1665, and 3330 mg/L.
Remark : The 30-minute EC50 value of 1950 mg/L is for the 20% APFO test solution. Based on 100% APFO, the EC50 value would be 390 mg/L.
Result : Test conditions:

Diluent: Millipore Milli-Q water
Test temperature: Not noted
Element basis: Percent light loss
Test substance : 20% solution in water of APFO (purity not specified)
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (51)

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 30 minute(s)
Unit : mg/l
EC50 : 3150
Analytical monitoring : no
Method : other: Microbics Microtox Basic Procedure
Year : 1996
GLP : no
Test substance : other TS

Method : Nominal concentrations include 0 (control), 625, 1250, 2500, and 5000 mg/L.
Remark : The 30-minute EC50 value of 3150 mg/L is for the 20% APFO test solution. Based on 100% APFO, the EC50 value would be 630 mg/L.
Result : Test conditions:

Diluent: Millipore Milli-Q water
Test Temperature: Not noted
Element basis: Percent light loss
pH of the stock solution: 6.0 (no adjustment)
Test substance : 20% solution of APFO in water (purity not specified)
Reliability : (2) valid with restrictions
The study lacks analytical confirmation of test substance concentrations.

08.12.2006 (50)

Type : other
Species Exposure : Paramaecium caudatum (Protozoa)
period : 4 day(s)
Unit : mg/l
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Paramecium caudatum is a protozoan that has been used to investigate the effects of chemicals on physiological processes. When cells are transferred to a K+-rich solution, increases in Ca2+ conductance by stimulation of Ca2+-channel results in initiation of backward swimming.

Cells begin whirling in consequence, when the increase in Ca2+ conductance is attenuated. Thus if a given chemical has some effects on the processes of Ca2+-channel kinetics, a series of swimming behavior will be modified. In the present study, the effects of PFOS and PFOA on K+-induced swimming behavior were investigated. After cultivating for 4 days, cells were transferred in K+-rich solution with PFOS or PFOA (1, 10, or 100 ppm in K+-rich solution) added and the cells were examined with a stereoscopy.

Result : In comparison with a period in the K+-rich solution, backward swimming was significantly prolonged by PFOS (60.7% at 1 ppm and 162.4% at 10 ppm versus 25.5% in controls); at 100 ppm, PFOS was lethal and all cells died within 5 minutes. PFOA prolonged backward swimming significantly only at 100 ppm (65.85%). The present study clearly demonstrated that PFOS has effects on Ca2+ conductance at pharmacological dose levels likely through an action on the cellular membrane. Since the Ca2+ signaling plays important roles in homeostasis, PFOS may perturb cellular functions through Ca2+ signaling.

Test substance : PFOA

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

08.12.2006 (641)

Type : aquatic
Species : activated sludge
Exposure period : 7 minute(s)
Unit : mg/l
EC50 : > 1000
Analytical monitoring : no
Method : other: Protocol Reference EAR, 11/8/79
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The only nominal concentration tested was 1000 mg/L. A blank control was also included.

Reliability : (3) invalid
Testing lacks record of methodology used. The study lacks analytical measurement of test substance concentrations in the test solutions.

08.12.2006 (32)

4.5.1 CHRONIC TOXICITY TO FISH

Species : Oncorhynchus mykiss (Fish, fresh water)
Endpoint : other: Early life stage
Exposure period : 85 day(s)
Unit : mg/l
NOEC : = 40
Analytical monitoring : yes
Method : OECD Guide-line draft "Early Life Stage Test (ELS-Test)"
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this study was to assess the lethal and sub-lethal effects of APFO on hatching and early-life stages (embryos, larvae and juveniles) of Oncorhynchus mykiss, under flow-through conditions, according to OECD Guideline (No. 210, 17th July 1992). The main criteria determined are the No and Lowest Observed Effect Concentrations (NOEC and LOEC) of the test item.

The concentrations used in this study were: 0 (control), 3.13, 6.25, 12.5, 25.0 and 50.0 mg/L nominal, expressed as the APFO (solids) content of the test item. An aliquot of each sample was diluted and analyzed by Ion Chromatography with Electrochemical Detection (Conductimetry). The concentrations of APFO were determined from a calibration curve of peak area against concentration of APFO in standard solutions.

Number of animals: 180 fertilized eggs per concentration divided into three replicates of 60 eggs each.

Result : Time of first hatching embryos in control: Day 24, first larvae at day 50. Harmonic means were calculated as 2.18, 4.48, 10.7, 20.9 and 40.0 mg/L expressed as the APFO (solids) content of the test item, for nominal values of 3.13, 6.25, 12.5, 25.0 and 50.0 mg/L, respectively.

The NOEC of APFO in a flow-through test system was 40.0 mg/L (highest mean measured concentration tested in this study), based on mortality and sub-lethal effects, for early-life stages of the rainbow trout Oncorhynchus mykiss.

Validity criteria:

• the hatching success was > 66% (81%) and the post-hatch success (until the end of the test) at least 70% in the control (88%),
• the dissolved oxygen concentration remained = 60% of the air saturation value throughout the test.
However:
• the temperature range for embryos (11.1°C to 12.5°C) was within the variation criterion of ± 1.5°C, but deviated slightly from the nominal range of 8°C to 12°C. The temperature range for larvae and juvenile fish (11.6°C to 14.4°C) was within the variation criterion of ± 1.5°C, but deviated slightly from the nominal range of 10°C to 14°C. This deviation was not considered to have affected the validity of the study,
• actual concentrations of the test item in test solutions were not maintained within ± 20% of the (harmonic) mean measured values. However, the means of the measured concentrations ranged from 70% to 85% of the nominals, and the coefficients of variation ranged from 18% to 33%, which were considered satisfactory.

Chemical analysis

Measured concentrations of the test item were not within ± 20% of the nominal values throughout the test. All study results were therefore based on harmonic means of measured concentrations in test solutions throughout the test (i.e. 85 days). These harmonic means were calculated as 2.18, 4.48, 10.7, 20.9 and 40.0 mg/L expressed as the APFO (solids) content of the test item, for nominal values of 3.13, 6.25, 12.5, 25.0 and 50.0 mg/L, respectively.

Mortality

According to analysis of variance (Dunnetts or Bonferroni test):
• the No Observed Effect Concentration (NOEC) based on mortality before hatching of larvae (egg and embryo stages) per replicate was 40.0 mg/L,
• the NOEC based on mortality of larvae per replicate was 40.0 mg/L. The NOEC based on mortality of juvenile per replicate could not be determined using analysis of variance since data failed to meet homogeneity of variance. This failure came from values obtained at 4.48 mg/L, which were the same in the three replicates. In this case, the Bartlett test can not determine homogeneity of variance. When the 4.48 mg/L group was discarded, data met homogeneity of variance and the NOEC based on

mortality of juvenile per replicate was 40.0 mg/L. A non-parametric method, i.e. the Wilcoxon rank sum test, confirmed this statistical result based on analysis of variance.

Sub-lethal effects

According to Dunn's test, using individual fish values as the unit of analysis after pooling of the replicate data:
• the mean weight of the fish was not significantly different from the control at any of the concentrations tested; therefore, the NOEC based on weight was 40.0 mg/L,
• the mean length of the fish was not significantly different from the control at the three highest test concentrations (10.7, 20.9 and 40.0 mg/L). A significant difference was identified at concentrations of 2.18 and 4.48 mg/L. However, no concentration related response trend was observed and the maximum reduction in mean weight compared to the control was less than 6%. Considering also the absence of significant effects on length at higher concentrations, and the absence of any significant differences in the weight of the fish, the apparent differences in length at the two lowest concentrations were considered to be chance occurrences. Therefore, the NOEC based on length was considered to be 40.0 mg/L.

In addition, the test item at concentrations up to and including 40.0 mg/L, did not delay significantly the hatching period of larvae.

Test conditions:

Dilution water:

Filtered and dechlorinated potable water which is then softened by a Permo® water softening system. Half of the water passes directly into a holding tank attached to the flow-through system while the remaining half passes through a deionizer producing ultra-pure water which is then fed into the holding tank. This results in a 1:1 dilution of potable dechlorinated:deionized water giving a supply of the desirable hardness. The pH of the solution is between 6.0 and 8.5 and the total hardness is 150 ± 20 mg/L as $CaCO_3$.

Minimum and Maximum Dilution water chemistry:

pH: 7.36 and 8.10
Hardness: 140 and 168 mg/L (as $CaCO_3$)
Temperature in test vessels:
11.1 and 12.5°C (eggs/embryos)
11.6 and 14.4°C (larvae/juvenile fish)
Dissolved oxygen: 83 and 100% (>60% of air saturation)

Test substance : 19.6% APFO in water
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2006 (123)

Species : Pimephales promelas (Fish, fresh water)
Endpoint : other: Survival, time to first oviposition, and male plasma 11-ketotestosterone, testosterone
Exposure period : 39 day(s)
Unit : mg/l
NOEC : > 74.1
Analytical monitoring : yes
Method : other
Year : 2004
GLP : no
Test substance : other TS

Method : This study investigates reproductive impairment and biochemical changes in fathead minnow (Pimephales promelas) exposed for 39 days to varying concentrations of perfluorooctanoic acid (PFOA) under microcosm conditions.

Nominal concentrations included 0 (control), 0.3, 1.0, 30, and 100 mg/L PFOA. Water samples were obtained in each microcosm at 1 hour, and 1, 2, 4, 7, 14, 21, 28, and 35 days after PFOA addition to calculate time-weighted mean PFOA concentrations over the course of the experiment. The PFOA concentrations were determined by ion chromatography.

Result : Analytical TWA concentrations were 0.27, 0.65, 23.9, and 74.1 mg/L, respectively for the nominal concentrations of 0.3, 1.0, 30, and 100 mg/L PFOA.

While the concentrations tested in this study were much higher than those normally found in the environment, no mortality was associated with PFOA exposure. Only modest changes were observed in condition factor and in relative liver and gonad size. Significant declines in circulating plasma steroids were observed, but these were accompanied by only limited increases in time to first oviposition and decreases in overall egg production. Peroxisome proliferation, as quantified by fatty acyl-CoA oxidase (FAO) activity, was elevated with low PFOA concentrations, but attenuated with exposure to higher PFOA doses. Little evidence was seen of differential induction of peroxisome- associated enzyme activity with sex. Oxidative stress, as quantified by the 2-thiobarbituric acid reactive substances (TBARS) assay, was only modestly influenced by PFOA exposure and is not a significant consequence of FAO activity in the fathead minnow. The NOEC for survival was greater than 100 mg/l; the NOEC for time to first oviposition was equal to 50 mg/l; the NOEC for male plasma 11-ketotestosterone and testosterone was 0.3 mg/L.

Dilution water: Irrigation pond supplied by on-site well
Dilution water chemistry: pH: 8.5 (Range 7.9-8.9)
Alkalinity: 112.9 mg/L (as $CaCO_3$); range 92.5-151.0 mg/L

Test conditions:

Maximum and minimum daily Temperatures:

Maximum: 21.7°C (range 11.6-26.6°C)
Minimum: 17.9 (range 10.6-20.8°C)

Dissolved oxygen: 7.6 mg/L (range 3.8-11.5 mg/L)

Test substance : Perfluorooctanoic acid was donated to the Centre for Toxicology (University of Guelph, ON, Canada) by the 3M Company as a 19.4% wet-weight aqueous solution. No analysis of the purity of the test substance was reported.

Reliability : (1) valid without restriction
Testing meets the criteria for quality testing, although sample purity may not have been properly characterized (no data were presented).

13.01.2006 (460)

Species : Pimephales promelas (Fish, fresh water)
Endpoint : other: Hatchability, survival, growth, and histopathology
Exposure period : 30 day(s)
Unit : mg/l
NOEC : > 100
Analytical monitoring : yes
Method : other
Year : 1978
GLP : no

Test substance : as prescribed by 1.1 - 1.4

Method : The following procedures for egg and fry stages of freshwater fishes followed at this laboratory, closely adheres to the proposed Recommended Bioassay Procedure for Egg and Fry Stages of Freshwater Fish (EPA, 1972).

Fathead minnow (Pimephales promelas) eggs and fry were continuously exposed to nominal APFO concentrations including 0 (control), 6.2, 12.5, 25, 50, and 100 mg/L through 30 days post-hatch. Observations were made on percentage hatch of eggs and on survival, mean total length and mean wet weight of fry.

Remark : Water samples were collected and sent to 3M for chemical analysis. However, no data on these determinations was found in this report.

Result : No adverse results were seen on percentage hatch of eggs and on survival, mean total length and mean wet weight of fry. Additionally, no compound-related histopathological changes were noted in the 30-day old fry.

Conc. [mg/L]	Hatch (%)	30d post-hatch survival
0	96.5	93.5
6.2	94.5	93
12.5	90.5	97.5
25	99	92.5
50	92.5	94
100	96	85

Dilution water chemistry:
pH range: 7.0-7.3
Hardness: 31-38 mg/L (as CaCO3)
Alkalinity: 26-32 mg/L (as CaCO3)
Temperature: 25°C
Dissolved oxygen: >95% of saturation

Reliability : (2) valid with restrictions
Testing meets the criteria for quality testing. However, sample purity was not properly characterized. While it is mentioned in the report that water samples were taken weekly from each test aquarium and sent to the sponsor for determination of the test substance, analytical confirmation of test substance concentrations was not presented.

08.12.2006 (242) (243)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 21 day(s)
Unit : mg/l
NOEC : 20
Analytical monitoring : yes
Method : OECD Guide-line 211
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The toxicity to reproduction of APFO was evaluated in the cladoceran, Daphnia magna Straus (clone 5) using a 21-day semi-static test according to OECD Guideline No. 211 (21st September 1998). The criterion of toxicity measured was the effect of the test item in solution on the reproductive

efficacy. This is expressed as: the EC50, the concentration required to reduce the number of living neonates per adult alive at the end of the test to 50% of the control value, the No Observed Effect Concentration (NOEC), obtained by analysis of variance from these data.

Five nominal concentrations of APFO were used together with a control at 0, 6.25, 12.5, 25.0, 50.0 and 100 mg/L expressed as the APFO (solids) content of the test item.

Water samples were taken for chemical analysis at the beginning of the test, before and after the medium renewals, and at the end of the test. An aliquot of each sample was diluted and analyzed by Ion Chromatography with Electrochemical Detection (Conductimetry). The concentrations of APFO were determined from a calibration curve of peak area against concentration of APFO in standard solutions.

Test solutions were changed every 2 or 3 days. Ten daphnids (ten individual replicates) were exposed to each concentration for 21 days and immobilization of adults and number of dead and living neonates were recorded daily throughout the test.

Dilution water: Reconstituted water (M4) prepared from deionized water with a conductivity of less than 10 uS/cm.

Result : Results (harmonic means of measured concentrations are found below):

Some measured concentrations were not within ± 20% of the corresponding nominal values. However, the maximum CV of the measured concentrations (at the beginning of the test and before medium renewals) at each of the different nominal target values was only 8.50% (at 6.25 mg/L nominal), indicating that the test item was sufficiently stable between medium renewals.

All study results were therefore based on harmonic means of measured concentrations in test solutions throughout the 21-day test. These harmonic means were calculated as 4.31, 9.16, 20.0, 44.2 and 88.6 mg/L expressed as the APFO (solids) content of the test item, for nominal values of 6.25, 12.5, 25.0, 50.0 and 100 mg/L, respectively.

Mortalities

The test item did not induce significant mortality in parent animals at concentrations tested. At the end of the test, the cumulative mortality in parent animals was 20% (2/10) in the control, 10% (1/10) at 4.31 mg/L, 0% (0/10) at 9.16 mg/L, 0% (0/10) at 20.0 mg/L, 10% (1/10) at 44.2 mg/L, and 10% (1/10) at 88.6 mg/L.

Reproduction

A significant inhibition of the reproduction capacity (expressed as the number of living neonates produced per parent alive at the end of the test) was obtained at 44.2 and 88.6 mg/L, compared to the control. The mean number of living neonates produced per parent alive at the end of the test in the control was 63.3.

The reproduction capacity values were as follows:
21-day EC50: 39.6 mg/L
No Observed Effect Concentration (21-day NOEC): 20.0 mg/L

Length

A significant inhibition of the length of parent animals (alive at the end of the test) was obtained at 88.6 mg/L, compared to the control.

The length values were as follows:
21-day EC50: > 88.6 mg/L
No Observed Effect Concentration (21-day NOEC): 44.2 mg/L

Environmental test parameters were:

• pH: 7.56 to 8.26,
• temperature: 18.4°C to 20.4°C,
• dissolved oxygen: 7.8 to 9.2 mg/L (> 3 mg/L throughout the test),
• water hardness: 255 to 289 mg/L as CaCO3.

Dilution water chemistry (as tested):

pH range: 7.56-8.26
Hardness: 255-289 mg/L (as CaCO3)
Temperature range: 18.4-20.4°C
Dissolved oxygen range: 7.8-9.2 mg/L

Test substance : 19.6% APFO in water
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2006 (121)

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 21 day(s)
Unit : mg/l
NOEC : 22
EC50 : 43
Analytical monitoring : no
Method : other: Semi-static life-style toxicity (see Method Information)
Year : 1984
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Survival and reproduction of APFO were evaluated in Daphnia magna using a 21-day semi-static test modeled after OECD (1981), EPA (1982), and ASTM (1983) guidelines (see below).
EPA (1982) EPA560/6-82-002 Environmental Effects Test Guidelines

OECD (1981) Guidelines for Testing of Chemicals

ASTM (1983) Proposed Standard Practice for Conducting Renewal Chronic Effects Tests with Daphnids

The criterion of toxicity measured was the effect of the test item in solution on the reproductive efficacy. This is expressed as: the EC50, the concentration required to reduce the number of living neonates per adult alive at the end of the test to 50% of the control value, the No Observed Effect Concentration (NOEC), obtained by analysis of variance from these data. Survival was also monitored.

Nominal test concentrations were 0 (control), 5, 8, 13, 22, 36, and 60 mg/L.

Test conditions:
Dilution water: Aerated, carbon-filtered well water

Result : Additional results:
14-day NOEC (survival) = 60 mg/L
14-day NOEC (reproduction) = 8 mg/L
21-day NOEC (survival) = 22 mg/L
14-day EC50 (reproduction) = 40 mg/L
No mortality of parent animals occurred in the control.

Dilution water chemistry (sampled one month prior to the study):

pH: 7.8
Hardness: 240 mg/L (as CaCO3)
Alkalinity: 230 mg/L (as CaCO3)
Temperature (during the test): 22°C
Dissolved oxygen: No information presented
COD: < 0.4 mg/L

Reliability : (2) valid with restrictions
The study was well conducted according to the methodology available at the time of test initiation. Information was not available on test substance purity and analytical analysis of the test concentrations was not conducted.

08.12.2006 (37)

Species : other: Mixed zooplankton
Endpoint : other: zooplankton species abundance and richness (number of different species)
Exposure period : 35 day(s)
Unit : mg/l
LOEC : 10 - 70
Analytical monitoring : yes
Method : other
Year : 2003
GLP : no
Test substance : other TS

Method : The zooplankton community consisted of following representative species: Cyclops diaptomus, Cyclops strenuus, Cyclops canthocamptus staphylinus, Daphnia magna, Keratella quadrata, Phyllopoda sp., Echninorhynchus sp., Ostracoda sp., and total Rotifera sp. In addition to zooplankton and pond snails, occasional macrophytes (Elodea canadansis and Myriophyllum spicatum) and larger invertebrates (Ephemeroptera sp., Asellus aquaticus) were present.

MICROCOSMS: 30 L (46x26x26 cm) PVC aquariums. Randomly filled with sediment (no further information), animals, phytoplankton (ca. 10E3 cells/mL) and clean water from the field. After 4 week stabilization period a sampling schedule was implemented: 24h pre-treatment, 24h post-treatment, 2, 4, 7, 14, 21, 28 and 35d post-treatment. Modified zooplankton funnel traps were used for pelagic sampling. Traps were suspended 3cm above the sediment floor in the middle of the aquariums. They consisted of a single 10 cm diameter reversed-funnel with a 60 mL confinement jar at the top and were set 24h before taking the actual sample to allow for sufficient animal collection. Animals were trapped during their cyclic vertical migration. On sampling days, confinement jars were homogenised by stirring and 30 mL of the trapped volume was fixed and preserved in Lugol's solution to be used for determination of zooplankton. Polyethylene and PVC equipment was used to reduce problems associated with adsorption of PFOA to glass. PFOA was carefully added to microcosm water and gently hand mixed in the aquariums with a plastic rod.

Test conditions:
Dilution water: Water taken from natural ponds at the University of Roskilde in Copenhagen, Denmark.

Nominal test concentrations were 0 (control), 1, 10, 20, 30, and 70 mg/L. The analysis of the water samples taken from the aquariums was done by Ion Chromatography (IC). Only the 10, 20, and 30 mg/L (nominal) samples were analyzed.

Result : The aim of this paper was to determine a 35 day community NOEC or lowest observable effect concentration (LOEC) for freshwater zooplankton

exposed to PFOA. Fluctuations in zooplankton abundance were observed, however, a NOEC could not be calculated. The overall analysis showed that, compared to controls, total zooplankton abundance was significantly increased at 1, 10, 20, and 30 mg/L, but not at 70 mg/L. However, the overall species richness was significantly reduced at 10, 30, and 70 mg/L indicating a simplification of the community structure. This was seen with a shift from a more diverse community with more total zooplankton species towards less richness where it was dominated by smaller zooplankton species (Rotifera sp.). LOEC for various species varied between 10 and 70 mg/L.

The study revealed that the representative rotifer species were insensitive to PFOA and actually increased in abundance. This could be the result of an improved competitive position relative to the other more sensitive zooplankton taxa.

According LOEC values the tentative order of descriptors sensitivity was as follows: Daphnia magna >richness > Cyclops canthocampus staphylinus > Cyclops diaptomus > total zooplankton > Rotifera sp.

The analysis of the water samples taken from the aquariums was done by Ion Chromatography (IC) utilizing a Dionex Corp. DX-500 IC system. Only the 10, 20, and 30 mg/L (nominal) samples were analyzed. Measured concentrations at day 35 were 11.32, 27.9, and 34.8 mg/L, respectively.

Dilution water chemistry:

pH: No information
Hardness: Moderately hard (°dH 8-12)
Temperature: 19°C
Dissolved oxygen: 6 mg/L

Test substance : 18.7% sodium salt of PFOA in water (as received); purity was not analyzed.

Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principles, and is acceptable for assessment.

13.01.2006 (537) (538)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

Species : other: Midge Chironomus tentans
Endpoint : other: growth and survival
Exposure period : 10 other: days
Unit : other: mg/L
NOEC : > 100
Method : other: EPA 600-R99-064 (Methods for measuring the toxicity and bioaccumulation of sediment-associated contaminants with freshwater invertebrates)
Year : 2004
GLP : no
Test substance : other TS

Method : This test was conducted as a range finding test. Therefore no analytical procedure was done. Ten midge were exposed to 100 mg/L of PFOA in a 10-day study. All experimental units were aerated. DOC remained consistently > 5mg/L for test duration (in the guidelines 2.5 mg/L is required as minimum). Environmental chamber conditions were 23°C, with a 16:8 hour light:dark photoperiod. Replicates for test were prepared one day before test start by adding 50 mL of clean culture sand to each 250 mL polypropylene beaker. Overlaying treatment solutions were prepared by

diluting concentrated PFOA stock solutions in control water. They were then gently poured along the sides of each beaker to a volume of approximately 240 mL. Replicates were then placed in environmental chambers and allowed to settle for 3 hours. Then 1.5 mL-aliquots of test food was added to each replicate. Animals were fed daily with this amount of food slurry.

Result : No effect on growth or survival was seen at a nominal concentration of 100 mg/L (the only concentration tested).

Test substance : PFOA (purity greater than 97%)

Reliability : (2) valid with restrictions
Study was well documented, meets generally accepted scientific principles, and is acceptable for assessment.

07.12.2006 (425)

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

Type : other
Species : Caenorhabditis elegans (Worm (Nematoda), soil dwelling)
Endpoint : other: fecundity and mobility
Exposure period : 48 hour(s)
Unit :
Method : other
Year : 2004
GLP : no
Test substance : other TS

Method : In the acute test, about 20 Caenorhabditis elegans larvae were poured onto a plate containing nominal concentrations of 0 (control), 0.01, 0.1, 0.5, 1.0, and 5.0 mM of the test chemical. The total number of worms and the number of active worms on each plate were counted at 1, 2, 3, 4, 24, and 48 hours after starting exposure to estimate mobility. All experiments were performed at 16°C without food in triplicate and repeated at least 3 times on different occasions. The median effective concentration (EC50) was calculated using the PROBIT method.

In the multi-generation test, E. coli DH5a was spread on the plates before the test. Then first generation Caenorhabditis elegans L1 larvae were poured onto each plate to start the test. When worms grew to L4 larvae, one worm was picked up and transferred to a new plate of the same composition and incubated at 16°C. The number of worms and eggs on the plates were counted at 24-hour intervals. The day when the first offspring was identified was defined as the first day of the test. The second- generation worms were allowed to grow to L4 larvae on the same plate, and then one worm was picked up and transferred to a new plate of the same composition. These steps were repeated until the fifth generation was cultured. These experiments were carried out in triplicate and repeated at least 3 times on different occasions.

Result : In an acute bioassay with Caenorhabditis elegans larvae, EC50 values for PFOA were 3.85 mM (1594 ppm) at 1 hour, 2.80 mM (1159 ppm) at 2 hours, 2.70 mM (1118 ppm) at 3 hours, 2.65 mM (1097 ppm) at 4 hours, 2.75 mM (1139 ppm) at 24 hours, and 2.35 mM (973 ppm) at 48 hours.

In a multi-generation test, PFOA affected the fecundity of Caenorhabditis elegans at concentrations 105- to 108-fold lower than the EC50 values (nominal concentrations used in the multi-generation study were 100 pM, 1 nM, and 10 nM [equivalent to 41.4, 414, and 4141 ppb, respectively]. In

particular, worm abundance during the first generation did not differ significantly from controls. Generation- and concentration-response relationships were not observed for PFOA, and the effects were almost the same in the second, third, fourth, and fifth generations.

For the endpoints worm abundance and egg production a NOEC of 1 nM (4.1x10-4 mg/l) and a LOEC of 10 nM (4.1x10-3 mg/l) was maintained.

Test substance : PFOA (purity not specified).
Reliability : (2) valid with restrictions
The purity of the test substance was not determined and the test concentrations were not analyzed.

08.12.2006 (598)

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Excretion
Species : laboratory animal
Number of animals
Males :
Females :
Doses
Males : 10 mg/kg of 14C-labelled C-8
Females : 10 mg/kg of 14C-labelled C-8
Vehicle : water
Route of administration : gavage
Exposure time : 168 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1:st
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A male and female of each species received a single 10 mg/kg dose of 14C-ammonium perfluorooctanoate via intragastric intubation. The rats, mice, and hamsters were housed individually in glass metabolism units immediately after dosing. Expired CO2, urine, and feces were collected at 12, 24, 48, 72, 96, and 120 hours after dosing. The male and female rabbits were individually housed in stainless steel metabolism cages immediately after dosing. Urine and feces were collected 24, 48, 72, 96, 120, 144, and 168 hours after dosing. Expired CO2 was not collected. Blood was drawn from the rabbits 168 hours after dosing. The rats, mice, and hamsters were all sacrificed 120 hours after dosing and blood was drawn. All animals were dissected with following tissues excised, weighed, and frozen: heart, lungs, liver, kidneys, spleen, testes or ovaries, brain, G. I. tract, and muscle, skin, and fat samples. The carcasses were then weighed and frozen. Metabolism units were washed and the cage washes were collected and refrigerated. Urine, CO2 samples, and cage washes were analyzed directly for radioactivity using a liquid scintillation counter. Blood, feces, tissues, organs, and homogenized carcass samples were analyzed for 14C content by tissue oxidation using a tissue oxidizer and liquid scintillation counter. Rabbit carcasses were not analyzed for 14C content.

Result : Sex and species differences in the excretion and disposition of radiolabeled C-8 were observed in a study in rats, mice, hamsters, and rabbits. The female rat and the male hamster excreted over 99% of the administered dose by 120 hours after dosing. Conversely, the male rat and the female hamster excreted 39 and 60% of the administered dose by 120 hours post-dosing. Both sexes of rabbits excreted the C-8 as rapidly and completely as the female rat and male hamster. The male and female mice excreted only 21% of the administered dose in 120 hours.

Test condition : Male and female rats, mice, hamsters, and rabbits were included in this study.

Test substance : 14C-labelled APFO

08.11.2005 (189)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males : 3
Females :
Doses
Males : 11 mg/kg
Females :
Vehicle : physiol. saline
Route of administration : gavage
Exposure time : 24 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st 4.8 days
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : This test was designed to provide total carbon-14 absorption and plasma elimination data in rats orally administered radiolabeled test material.
Result : After a single oral dose of FC-143-14C (mean dose, 11.0 mg/kg) in solution to groups of 3 male rats, at least 93% of the total carbon-14 is absorbed at 24 hours. The half-life of elimination of total carbon-14 from plasma is 4.8 days.
Test substance : 14C-labeled APFO
25.10.2005 (516)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males : 6
Females : 5
Doses
Males : 13.1 mg/kg
Females : 16.7 mg/kg
: physiol. saline
Route of administration : i.v.
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests :
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Male and female rats were conditioned to individual metal metabolism cages for 24 hours prior to dosing. Each rat was weighed, lightly

anesthetized, and then given a single iv dose (via tail vein) of radiolabeled test material. Urine and feces were collected at intervals for each of the female rats for 17 days and for each of the male rats for 36 days. Blood was taken from each rat at the time of sacrifice. Feces and major organs were prepared for carbon-14 analysis.

Result : A very extensive sex difference in extent and rate of excretion of total carbon-14 was observed between male and female rats after a single iv dose (mean dose: female, 16.7 mg/kg; male, 13.1 mg/kg) of FC-143-14C. Female rats excreted essentially all of the dose via urine in 24 hours while at the same time period, male rats excreted only 20% of the dose; male rats excreted 83% via urine and 5.4% via feces by 36-days post-dose. No radioactivity was detected in tissues of female rats at 17 days post-dose; male rats had 2.8% of the dose in the liver and 1.1% in plasma at 36 days post-dose with smaller levels (0.5% or less of the dose) in other organs.

Test substance : 14C-labeled APFO

25.10.2005 (517)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females : 6
Doses
Males :
Females : 15 mg/kg
: physiol. saline
Route of administration : gavage
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Female rats were bred at 8 or 9 days prior to dosing. The rats were conditioned to individual metal metabolism cages for 24 hours prior to dosing. Each rat was given a single oral dose of radiolabeled test material. Urine samples were collected for each rat from 0-12, 12-24, 24-36, and 36-48 hours post-dose.

Remark : There were 4 pregnant rats and 2 non-pregnant rats in the test group.

Result : Hormonal changes during pregnancy do not appear to cause a change in the rate of elimination of carbon-14 after oral administration of a single dose of ammonium 14C-perfluorooctanoate (mean dose, 15 mg/kg). At 8 or 9 days after conception, 4 pregnant rats and 2 non-pregnant female rats were dosed and individual urine samples were collected at 12, 24, 36, and 48 hours post-dose and analyzed for carbon-14 content. Essentially all of the carbon-14 was eliminated via urine within 24 hours for both groups of rats. These data are consistent with previously reported data for non-pregnant rats. Thus, there is not likely to be any accumulation of 14C-perfluorooctanoate in tissues of pregnant rats during repeated dosing in teratology studies.

Test substance : 14C-labeled APFO

16.11.2005 (524)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males : 5
Females :
Doses
Males : 13.3 mg/kg
Females :
Vehicle : physiol. saline
Route of administration : i.v.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Cholestyramine, an agent approved for use in humans to lower cholesterol blood levels, is an anion exchange resin which has been administered orally to promote fecal excretion of the pesticide chlordecone (Kepone) in rats and man. Since FC-95 and FC-143 are perfluorinated salts and exist as anions at physiologic pH, they would be expected to complex with cholestyramine. Non-ionic binding could also be involved. This experiment in rats was designed to assess the effect of cholestyramine treatment on C-14 elimination and tissue retention after iv dosing with FC-95-14C and FC-143-14C. Rats were fed cholestyramine in feed for 14 days after the administration of radiolabeled ammonium perfluorooctanoate. Control rats were administered radiolabeled ammonium perfluorooctanoate but were not treated with cholestyramine. The rats were sacrificed at day 14 and the mean liver, plasma, and red blood cell concentrations as well as fecal and urinary excretion of FC-143-14C determined and compared to those of the controls.

Result : After a single i.v. 13.3 mg/kg dose of radiolabeled ammonium perfluorooctanoate, cholestyramine fed daily as a 4% mixture in feed was shown to increase the total radioactivity eliminated via the feces and to decrease the liver concentration of radioactivity. Rats were fed cholestyramine in feed for 14 days after the administration of radiolabeled ammonium perfluorooctanoate. Control rats were administered radiolabeled ammonium perfluorooctanoate but were not treated with cholestyramine. Cholestyramine treatment increased mean cumulative radioactivity in the feces by 9.8-fold. After radiolabeled ammonium perfluorooctanoate, a mean of 4% of the dose of was in the liver of cholestyramine-treated rats at 14 days versus 7.6% in control rats. Plasma and red-blood cell concentrations of radiolabeled ammonium perfluorooctanoate, which were relatively lower than liver concentrations, were also significantly reduced by cholestyramine treatment.

Test substance : 14C-labeled FC-143

25.10.2005 (518)

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males :

Females	:	2
Doses		
Males	:	
Females	:	10 mg/kg
	:	

Route of administration : gavage
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1982
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 14C-labeled ammonium perfluorooctanoate was labeled on the carbonyl position and had a specific activity of 0.5 uCi/mg. Water was used as the dosing vehicle. The pregnant female rats received a single 10 mg/kg dose of 14C-labeled ammonium perfluorooctanoate by gavage on the 19th day of gestation. The rats were individually placed in glass metabolism units immediately after dosing. Two rats were sacrificed at each time interval of 2, 4, and 8 hours after dosing. Blood was drawn at sacrifice and refrigerated. The placentas, umbilical cords, and fetuses were then removed, dissected from each other, and weighed. The umbilical cords and placentas were individually placed into paper combustion cones and fetuses were frozen. Organs and tissues were also excised, weighed, and frozen. The carcasses were also weighed and frozen. Urine and fecal samples excreted between dosing and sacrifice were collected and frozen. The metabolism units were washed successively with dilute detergent, water, and acetone. The washes were collected and stored. The placentas, umbilical cords, and fetuses were oxidized in their entirety. Samples of the maternal tissues, carcass, and feces were also oxidized and analyzed for 14C activity by liquid scintillation counting. The urine and cage washes were analyzed directly by liquid scintillation counting.

Result : Radioactive 14C-labelled perfluorooctanoate (C-8) was transferred from, maternal blood to the fetuses of pregnant rats. A single 10 mg/kg dose of 14C-labelled C-8 was administered orally by gavage to the pregnant dams on the 19th day of gestation. Maternal blood and placental levels of 14C-labelled C-8 increased between 2 and 4 hours after dosing then decreased between 4 and 8 hours after dosing. The ug equivalents of 14C-labeled C-8 per mL of maternal blood were approximately 12 ug/mL at 2 hours, 20 ug/mL at 4 hours and 12 ug/mL at 8 hours after dosing. The fecal levels were 0.7 ug/g tissue at 2 hours, 3 ug/g tissue at 4 hours and approximately 3 ug/g tissue at 8 hours after dosing. All other tissues from the pregnant dams were examined for 14C activity and exhibited trends similar to maternal blood, increasing between 2 and 4 hours and decreasing between 4 and 8 hours after dosing. The data reflected only minimal impedance for transfer of 14C-labelled C-8 from maternal blood to the fetuses.

16.11.2005 (188)

In Vitro/in vivo : In vivo
Type : Excretion
Species : laboratory animal
Number of animals
Males : 5
Females :
Doses

Males : 10 mg/kg
Females :
: water
Route of administration : gavage
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests :
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 14C-Ammonium perfluorooctanoate (0.5 uCi/mg) as an aqueous solution was administered by intragastric intubation to 8 young adult male rats and 6 adult male mice at a dose of 10 mg/kg. One control group (2 rats and 2 mice) was sacrificed at 24 hours and 1 control group (3 rats and 2 mice) was sacrificed at 96 hours. The treated group (3 rats and 2 mice) was dosed with cholestyramine (1000 mg/kg) 24 hours after dosing with the test substance and then sacrificed at 96 hours. After dosing, rats and mice were placed in individual glass metabolism chambers. Exhaled 14C was sampled at 24, 48, 72, and 96 hours. Feces and urine were collected. At sacrifice time, 1-2 mL of blood was removed from the mice and approximately 8 mL of blood was removed from the rats. Livers were removed, homogenized, weighed, and 0.5 g samples were oxidized and counted.
Remark : The test group was comprised of 3 male rats and 2 male mice.
Result : Adult male rats and mice were given cholestyramine resin (Dowex Ion Exchange Resin) 24 hours after dosing with 14C-APFO. Although a previous study indicated that cholestyramine resin could reduce the acute lethal effects of C-8, there was no sign of enhanced elimination of 14C-C-8 via the feces, urine, or exhaled air.
Test substance : 14C-labeled APFO
08.11.2005 (186) (492)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1981

GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Female albino rats (7-8 weeks old and weighing approximately 200 g); pregnant primigravida females (weighing approximately 200 g); and male rats (approximately 8 weeks old and weighing approximately 250 g) were used. The rats were housed 2/cage and allowed food and water ad libitum.

Groups A-E rats were tested to measure blood organofluoride levels in female rats as a function of post-exposure time following oral administration and to investigate multiple versus single doses. Group A (21 female rats) was dosed with 25 mg/kg orally and 3 rats were sacrificed at ¼, ½, 1, 2, 4, 8, and 24 hours after dosing. Groups B and C (12 female rats/group) were orally dosed with 2.5 or 150 mg/kg, respectively, and 3 rats were sacrificed at ½, 2, 8, and 24 hours after dosing. Group D (21 female rats) was dosed 11 days with 25 mg/kg orally each day and 3 rats were sacrificed at ¼, ½, 2, 4, 8, 24, and 168 hours after the 11th dose. Group E (12 male rats) was dosed at 25 mg/kg orally and 3 rats were sacrificed at ½, 8, 24, and 168 hours after dosing.

Groups F-I rats were tested to measure blood organofluoride levels in female rats following inhalation exposure. Group F (24 female rats) was exposed to a single 6-hour exposure of 10 mg/m3 and 3 rats were sacrificed at ¼, ½, 1, 2, 4, 8, 24, and 168 hours after exposure. Groups G and H (12 female rats/group) were exposed to a single 6-hour exposure of 1 mg/m3 or 0.1 mg/m3, respectively, and 3 rats were sacrificed at ½, 2, 8, and 24 hours after exposure. Group I (12 male rats) was exposed to a single 6-hour exposure of 10 mg/m3 and 3 rats were sacrificed at ½, 2, 8, and 24 hours after exposure.

Groups J-N were tested to compare blood organofluoride levels in pregnant versus non-pregnant rats and to compare oral exposure versus inhalation exposure. Group J (12 pregnant female rats) was administered 25 mg/kg orally on gestation day 15 and 3 rats were sacrificed at ½, 2, 8, and 24 hours after dosing. Group K (6 pregnant female rats) was administered 25 mg/kg orally on gestation days 6-11 and 3 rats were sacrificed at ½ and 2 hours after the 6th dose. Group L (12 pregnant female rats) was administered 25 mg/kg orally on gestation days 6-15 and 3 rats were sacrificed at ½, 2, 8, and 24 hours after the 10th dose. Group M (6 pregnant female rats) was exposed via a single 6-hour inhalation exposure to 10 mg/m3 on gestation day 15 and 3 rats were sacrificed at ½ and 2 hours after exposure. Group N (3 pregnant female rats) was exposed via inhalation, 6 hours/day, to 10 mg/m3 on gestation days 6-15 and 3 rats were sacrificed at ½ hour after the 10th exposure. Blood samples were obtained from each rat.

Remark : Male and non-pregnant female rats as well as pregnant rats are included in this study.

Administration is by gavage and inhalation.

Result : The uptake and clearance of C-8 from the blood of female rats following a single oral dose was rapid with the peak reached one-two hours post-treatment and with virtual total clearance by 24 hours. A dose-response was demonstrated with no apparent changes in blood C-8 levels following multiple oral dosing. The slower clearance rate in male rats was demonstrated following a single oral dose. The same general statements apply following inhalation exposure. A single six-hour inhalation exposure resulted in peak blood levels within one hour after cessation of exposure, the material rapidly cleared from the blood, the number of exposures did not affect blood levels, and male rats cleared the compound much more slowly. Pregnant and non-pregnant rats showed similar C-8 blood levels following either oral or inhalation exposures.

In Vitro/in vivo : In vivo
Type : Absorption
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The concentration of organic fluorine in blood was determined by subtracting the inorganic fluoride concentration from total fluorine concentration. The latter was determined by gas chromatography, following combustion of the sample by a modified oxygen bomb technique. PFOA was also determined by gas chromatography following its extraction from serum and conversion to its methyl ester using diazomethane.
Result : Perfluorooctanoic acid has a long half-life in humans. A study of occupationally exposed workers at a plant which produces C-8 showed organic fluorine levels in the blood ranging from 1 to 71 ppm. One worker with a level of 70 ppm was removed from the fluorochemical production area and his blood analyzed for organic fluorine over several months. After 18 months, his organic fluorine level had decreased only to 39 ppm [45% reduction].

25.10.2005 (603)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : monkey
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : other: Capsule and i.v.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2004
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The pharmacokinetics of perfluorooctanoate (PFOA) in cynomolgus monkeys were studied in a six-month oral capsule dosing study of ammonium perfluorooctanoate (APFO) and in a single-dose iv study. In the oral study, samples of serum, urine, and feces were collected every two weeks from monkeys given daily doses of either 0, 3, 10, or 20 mg APFO/kg. In the iv study, three monkeys per sex were given a single dose

Result : of 10 mg/kg potassium PFOA. Samples were collected through 123 days. Steady-state was reached within four weeks in serum, urine, and feces. Serum PFOA followed first-order elimination kinetics after the last dose, with a half-life of approximately 20 days. Urine was the primary elimination route. Mean serum PFOA concentrations at steady state in the 3, 10, and 20 mg/kg/day dose groups, respectively, were 81, 99, and 156 ug/mL in serum; 53, 166, and 181 ug/mL in urine; and, 7, 28, and 50 ug/g in feces. Mean liver concentrations reached 16, 14, and 50 ug/g in the 3, 10, and 20 mg/kg groups, respectively.

In the iv study, three monkeys per sex were given a single dose of 10 mg/kg potassium PFOA. Samples were collected through 123 days. The terminal half-life of PFOA in serum was 13.6, 13.7, and 35.3 days in the three male monkeys and 26.8, 29.3, and 41.7 days in the three females. Volume of distribution at steady state was 181 +/- 12 and 198 +/- 69 ml/kg for males and females, respectively.

Based on the result of both the oral and iv studies, the elimination half-life is approximately 14-42 days, and urine is the primary route of excretion.

16.11.2005 (110)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Perfluorooctanoic acid (PFOA) is an organic fluorochemical, and its elimination in rats is markedly sex-dependent. Liver and kidney are two primary tissues of distribution of PFOA in rats. In this study, the subcellular distribution of PFOA in male and female rat liver and kidney was examined.

Result : The results demonstrated that PFOA content in the liver cytosol of the female rat was significantly higher (49 +/- 6% of total radioactive residues, TRR) than in the male liver (26 +/- 5% TRR), whereas PFOA distribution in the heavier subcellular fractions, especially the nuclei and cell debris fraction, was marginally higher in male rat liver. In rat kidney, more than 70% of PFOA was distributed in the cytosolic fraction, with no significant difference between sexes. The degree of protein binding of PFOA in rat liver and kidney cytosol was analyzed by two different chromatographic methods. The percentage of protein-bound PFOA in the liver cytosol was found to be approximately 55% in both male and female rats. In contrast, significantly more PFOA was bound to cytosolic proteins in the kidney of male rats (42 +/- 6% TRR) than in females (17 +/- 5% TRR). Ligand blotting analysis revealed that multiple proteins from the liver cytosol, nuclei, and mitochondria fractions were capable of specific binding to PFOA.

Test substance : PFOA

08.11.2005 (295)

In Vitro/in vivo : In vitro
Type : Excretion
Species :
Number of animals

Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : Two male rat specific proteins, liver- and kidney-form alpha2u-globulins (A2U(L) and A2U(K)), were purified from male rat urine and kidney, respectively. The binding of these two proteins to PFOA was investigated using ligand blotting, electrospray ionization mass spectrometry and fluorescence competitive binding assay.

Result : Perfluorooctanoic acid (PFOA) is an organic fluorochemical and is reported to have a long half-life in human blood. Its urinary elimination in rats is markedly sex-dependent, and characterized by significantly longer plasma half-life of PFOA in male rats than in females. It has been postulated that male-specific PFOA binding protein(s) is responsible for the long half-life of PFOA in male rats. The results revealed that both A2U(L) and A2U(K) were able to bind PFOA in vitro under physiological conditions, and that PFOA and a fluorescent-labeled fatty acid shared the same binding site on both A2U(L) and A2U(K). The binding affinities, however, are relatively weak. The estimated dissociation constants are in the 10-3 M range, indicating that bindings of PFOA to either A2U(L) or A2U(K) cannot adequately explain the sex-dependent elimination of PFOA in rats, and it is unlikely that PFOA-A2U(K) binding would induce A2U nephropathy as seen with, for example, 1,4-dichlorobenzene.

Test substance : PFOA

16.11.2005 (294)

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females : 3, 10, or 30 mg/kg/day
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Three dose levels of 3, 10 and 30 mg/kg, along with a control dose containing no test substance, were administered to groups of 20 rats each. Formulations of test substance in deionized water were administered once daily by oral gavage at a dosing volume of 5 mL/kg; all formulations were

adjusted for sample purity (%). The control group recovered 5 mL/kg deionized water. Upon arrival, dams were ranked on the basis of day 0G body weights and assigned to control and experimental groups by random sampling from the ranked list. The distribution resulted in mean body weights for all groups that were not statistically different. Rats in each group were then randomly assigned to each subset. Daily dosing continued until scheduled sacrifice at days 10G, 15G, 21G and 21PP. Dose volumes were adjusted daily based on body weights.

On days 10, 15, and 21G, rats assigned to the particular subset were euthanized by carbon dioxide inhalation. For each female with visible implantation sites, the intrauterine location of each embryo/fetus and implantation type (live or early resorption) were recorded. A gross examination of maternal viscera was done and blood samples from each dam were collected from the vena cava and processed to obtain plasma. On day 21G, fetuses were euthanized with an overdose injection (i.p.) of sodium pentobarbital, and fetal blood samples were taken from a transverse cut made to the carotid artery. To allow maximal detection of PFOA at all doses in the current study, samples were collected approximately 2 hours post-dose to be close to the Cmax.

Samples collected in each sub-group were as follows: 10G maternal blood and whole embryos; 15G maternal blood, amnionic fluid, placentas, and whole embryos; and, 21G maternal blood, amnionic fluid, placentas, whole fetuses and fetal blood. Maternal blood samples were collected 2 hours post-dose; other tissues were collected as soon as possible after maternal blood collection. All embryos, fetuses, placentas and fetal blood were pooled by litter.

On days 3, 7, 14 and 21PP, maternal milk and blood samples were collected at 2 hours post-dose. Dams were removed from their litters approximately 1-2 hours before blood and milk samples were collected. Dams were anesthetized by isofluorane inhalation. Blood samples were collected from the orbital sinus and dams were returned to their litters after recovery from anesthesia. On day 21PP, maternal blood samples were taken from the vena cava. In addition, one pup per litter (two at day 21PP) was randomly selected, euthanized and a blood sample taken from a transverse cut made to the carotid artery (days 3 and 7PP) or from the vena cava (days 14 and 21PP).

Milk samples were collected after the blood sample collection. Oxytocin was administered by intraperitoneal injection to promote milk ejection from the mammary gland. Approximately 2-5 minutes after injection, the dam's nipple area was washed with warm saline or water. Milk was collected from more than one mammary gland; mammary glands were changed frequently and were repeated as necessary. Milk was collected by applying pressure to the entire base of the gland, pushing milk towards the nipple and into a test tube. Pups were kept in polycarbonate pans with bedding during the milk collection procedure. On day 3PP, litters were kept warm during the absence of the dam by the use of either a circulating hot water pad, heated gel packs, or heat lamp.

All prepared biological samples were analyzed by high-performance liquid chromatography followed by mass spectrometry. Plasma, milk, and amniotic fluid samples (pooled by litter) were processed by protein precipitation.

Placenta samples (pooled by litter) were coarsely chopped using scissors, prepared, and analyzed. Fetus samples were pooled by litter and homogenized using a Waring blender in the presence of liquid nitrogen, prepared, and analyzed.

Test formulations of PFOA were prepared and collected for uniformity of mixing/concentration verification and stability analysis three times during the dosing portion of this experiment. In addition, 0 mg/mL (control) samples were submitted for analysis with each set of samples.

Result : This study was conducted to develop a quantitative understanding of the potential for gestational and lactational transfer of perfluorooctanoate (PFOA) in the rat. Time-mated female rats were dosed by oral gavage once daily at concentrations of 3, 10, or 30 mg/kg/day of the ammonium salt of PFOA (APFO) starting on gestation (G) day 4 and continuing until sacrifice. On days 10, 15, and 21G, five rats per dose level were sacrificed and blood samples were collected 2h post-dose. Embryos were collected on day 10G, amniotic fluid, placentas, and embryos/fetuses were collected on days 15 and 21G, and fetal blood samples were collected on day 21G. Five rats per dose level were allowed to deliver and nurse their litters, and on days 3, 7, 14, and 21 post-partum (PP) milk and blood samples of maternal and pup were collected 2h post-dose. All samples were analyzed by high-performance liquid chromatography-mass spectrometry (HPLC-MS) for PFOA concentration. Concentrations of PFOA in maternal plasma and milk attained steady state during the sampling interval. The steady-state concentrations in maternal plasma were 10-15, 25-30, and 60-75 microg/mL in rats receiving 3, 10, and 30 mg/kg, respectively. Steady-state concentrations in milk were approximately 10 times less than those in maternal plasma. The concentration of PFOA in fetal plasma on day 21G was approximately half the steady-state concentration in maternal plasma. The milk concentrations appeared to be generally comparable to the concentrations in pup plasma. Pup plasma concentrations decreased from day 3PP to day 7PP, and were similar on days 7, 14, and 21PP at all dose levels. PFOA was detected in placenta (days 15 and 21G), amniotic fluid (days 15 and 21G), embryo (days 10 and 15G), and fetus (day 21G). These pharmacokinetics allow estimation of the dose to developing and nursing rat offspring following maternal exposure.

08.11.2005 (221) (320) (451)

In Vitro/in vivo : In vivo
Type : Distribution
Species : mouse
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : The tissue distribution of perfluorooctanoic acid (PFOA), which is known to show unique biological responses, has been visualized in female mice by 19F magnetic resonance imaging (MRI) incorporated with the recent advances in microimaging technique. The chemical shift selected fast spin-echo method was applied to acquire in vivo 19F MR images of PFOA. The in vivo T1 and T2 relaxation times of PFOA were proven to be extremely short, which were 140 (± 20) ms and 6.3 (± 2.2) ms, respectively To acquire the in vivo 19F MR images of PFOA, it was necessary to optimize the parameters of signal selection and echo train length. The chemical shift selection was effectively performed by using the 19F NMR signal of CF3 group of PFOA without the signal overlapping because the chemical shift difference between the CF3 and neighbor signals reaches to 14kHz. The most optimal echo train length to obtain 19F images efficiently was determined so that the maximum echo time (TE) value in the fast spin-

echo sequence was comparable to the in vivo T2 value.

Result : By optimizing the parameters desribed in the method, the in vivo 19F MR image of PFOA was enabled to obtain efficiently in 12 minutes. As a result, the time course of the accumulation of PFOA into the mouse liver was clearly pursued in the 19F MR images. Thus, it was concluded that the 19F MRI becomes the effective method toward the future pharmacological and toxicological studies of perfluorocarboxylic acids.

Test substance : PFOA

08.11.2005 (376)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males :
Females :
Doses
Males : 1, 5, and 25 mg/kg
Females : 1, 5, and 25 mg/kg
Vehicle :
Method : other: OECD Section 4: Toxicokinetics, No. 417 (1984)
Year : 2003
GLP : yes
Test substance : other TS

Method : The purpose of this study was to characterize the absorption, distribution, elimination and pharmacokinetic behavior of PFOA in male and female rats. Male and female CD rats were administered 14C-PFOA (carbonyl label) by oral gavage at dose levels of 1, 5, and 25 mg/kg. Urine and feces were collected for 28 days in males and 7 days in females, and tissues were analyzed for residual radioactivity at sacrifice.

Result : Urine was the primary route of elimination for 14C in both sexes. In males, urinary excretion accounted for approximately 43-62% of the administered dose. In females, the extent of urinary elimination was greater, accounting for approximately 76-84% of the administered dose. In males, fecal excretion of 14C accounted for approximately 6-14% of the administered dose, while in females, approximately 2-6% of the dose was recovered in feces. Pilot experiments demonstrated that 14C was not eliminated as either 14CO2 or volatile organic compounds in 14C-PFOA-treated rats. At sacrifice, approximately 13-24% of the dose remained in the tissues of male rats, while females retained less than 0.25% of the dose at any dose level. The highest concentrations of residual 14C were found in the blood, liver and kidney. Overall mean recovery of radioactivity ranged from 83.8 to 91.6% in males and 81.3 to 93.3% in females. Pretreatment of rats with 1 mg/kg PFOA for 14 days had little or no effect on excretion or terminal tissue distribution of a challenge dose of 1 mg/kg 14C.

The pharmacokinetic behavior of PFOA was investigated following oral administration of PFOA at dose rates of 0.1, 1, 5, and 25 mg/kg PFOA, and after intravenous administration of 1 mg/kg PFOA. Plasma was collected for 22 days after dosing in males and 5 days in females. Concentration vs. time data were analyzed by non-compartmental pharmacokinetic methods. Comparison of AUC for the oral and intravenous 1 mg/kg doses indicated that oral bioavailability of PFOA was approximately 100%. Plasma elimination curves were linear with respect to time in male rats at all dose levels, while elimination kinetics were biphasic in females at the 5 mg/kg and 25 mg/kg dose levels. In males, plasma elimination half-lives were independent of dose level and ranged from approximately 138 hours to 202 hours. In females, terminal elimination half-lives ranged from approximately 2.8 hours at the lowest dose to approximately 16 hours at the high dose. To further characterize plasma elimination kinetics, particularly in male rats, animals were given oral PFOA at a rate of 0.1

mg/kg, and plasma samples were collected until PFOA concentrations fell below quantitation limits (24 hours and 2016 hours in females and males, respectively). Estimated plasma elimination half-lives in this experiment were approximately 277 hours in males and 3.4 hours in females.

The tissue distribution of 14C at the time corresponding to maximum plasma concentrations (Tmax) and at the time corresponding to a return to 50% of maximum plasma concentration following attainment of maximum concentrations (Tmax/2) was investigated following administration of 1, 5, and 25 mg/kg 14C- PFOA. Tissues were collected at 10.5 and 171 hours after dosing in male rats and at 1.25 and 4 hours after dosing in female rats. For both sexes and at both sampling times, the major tissues for distribution of 14C were liver, kidney and blood. In males, the fraction of the dose found in liver increased from Tmax to Tmax/2, but remained constant or decreased in other tissues. In females, the fraction of the dose present in all tissues remained constant or decreased between Tmax and Tmax/2. Liver:blood concentration ratios for 14C at Tmax in males were greater than 1, and increased between Tmax and Tmax/2. Kidney:blood concentration ratios at Tmax in females were approximately 2 at all dose levels and remained relatively constant between Tmax and Tmax/2.

Overall, the results of this study demonstrated significant sex differences in excretion, pharmacokinetics, and tissue distribution of PFOA in rats.

Test substance : PFOA

08.11.2005 (224) (369)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males :
Females :
Doses
Males : 0, 1, 10, and 25 mg/m3
Females : 0, 1, 10, and 25 mg/m3
Vehicle :
Route of administration : inhalation
Exposure time : 6 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2003
GLP : yes
Test substance : other TS

Method : The study was comprised of two separate experiments: Phase I consisted of a single 6-hour nose-only exposure while Phase II consisted of repeated exposures (6 hours per day, 5 days per week for 3 weeks). In both experiments, male and female rats were exposed nose only to an aerosol of 0, 1, 10, or 25 mg/m3 PFOA. Levels were selected to produce plasma concentrations similar to those observed in previous oral gavage studies. In Phase I, blood was drawn via the tail vein pre-exposure, during exposure at 0.5, 1, 3 and 6 hours, and post-exposure at 1, 3, 6, 12, 18 and 24 hours. Rats were not removed from the exposure chamber during the exposure period and blood was taken from the tail vein while the animals remained in the nose-only restrainers attached to the exposure chamber. For Phase II,

blood was collected immediately before and after the daily inhalation exposure period three days per week. Plasma derived from the whole blood samples was analyzed by liquid chromatography-mass spectrometry (LC-MS).

Result : PFOA appears rapidly in the blood of both male and female rats exposed via the inhalation route. PFOA elimination is sex-dependent, with female rats eliminating PFOA from the plasma much more efficiently than male rats. PFOA plasma concentrations are proportional to the inhalation exposure concentrations from 1 to 25 mg/m3. Repeated daily inhalation exposures produce little plasma carryover in female rats, but significant carryover in male rats. Male rats reach a steady state plasma concentration by three weeks with plasma concentrations of 8, 21, and 36 µg/mL respectively for the 1, 10, and 25 mg/m3 exposures. Female rats reached post-exposure plasma concentrations of 1, 2, and 4 µg/mL respectively for the 1, 10, and 25 mg/m3 exposures, but returned to baseline levels for the pre-exposure time points.

Test substance : PFOA

08.11.2005 (219) (319)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : To investigate the T1/2 of serum elimination of PFOA in humans, 27 retirees (25 males and 2 females) from 2 fluorochemical manufacturing plants were followed for 5.5 years for periodic blood collections. The analysis for PFOA used a primary acid excretion in combination with an alkaline back extraction technique. A 5 uL injection was introduced to the mass spectrometer through a high performance liquid chromatography system. All quantitative calculations were based on the ion ratios between PFOA and the internal standard (dual substituted 13C-PFOA). The primary standard was a mixture of linear and branched chain isomers of PFOA. A total of 464 serum samples were analyzed. One retiree's samples were excluded due to the likelihood of occupational exposure to PFOA during follow-up.

Result : Initial serum concentrations of PFOA for the remaining 26 retirees ranged between 0.07 to 5.10 mg/mL. Only linear chain PFOA was observed. Individual serum elimination rates were calculated. The mean T1/2 of serum elimination was 1378 days (standard deviation 609) and ranged between 561 and 3334 days. Median was 1257 days (3.5 years). The T1/2 of serum elimination was not associated with initial PFOA concentrations, age or sex of retiree, years worked at the manufacturing facility, or the time between retirement and first blood collection.

Test substance : PFOA

19.10.2005 (244)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :

Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : First, the concentrations of PFOA and PFOS were measured in the serum of subjects who had lived in Kyoto City (Japan) for more than 10 years. Second, the renal clearances were determined for PFOA and PFOS in young (2-40 years of age, n = 5 for each sex) and old (60 years of age or more, n = 5 for each sex) subjects of both sexes.

Result : The serum concentrations of PFOA and PFOS increased with age in females but not in males. The levels in females caught up in males at ages 60 years or more. All the young females had menstruation cycles while the old females did not. The renal clearances were 10(-5)-fold smaller than the glomerular filtration rate, suggesting almost absence of renal excretion in humans. The sex differences in renal clearance that have been observed in rats and monkeys, were not found in humans. Renal clearance of PFOA in humans was about 1000 times lower than in rats and monkeys. The lower serum levels of PFOA and PFOS in females than in males might be associated with elimination through menstruation.

Test substance : PFOA

16.11.2005 (305) (306)

In Vitro/in vivo	:	In vivo
Type	:	Metabolism
Species	:	mouse
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : The metabolism of telomer alcohol was investigated in mice. Male CD-1 mice received a gavage dose of 20 mg/kg of 8-2 telomer alcohol dissolved in propylene glycol/water (1:1). Animals were serially sacrificed at 1, 3, 6, 12, and 24 hours post-treatment and organs excised for perfluorinated compound analysis. Telomer alcohol and metabolites were analyzed with EI-GC/MS.

Result : Based on preliminary studies, the telomer alcohol temporally decreased becoming non-detectable by 12 hours in both liver and serum. In liver, the telomer alcohol was seen at peak concentrations at 1 hour and in serum was quantified only at 1 and 3 hours. In serum, the most abundant metabolite was PFOA with a concentration of 186-212 ng/mL at 6 hours post-treatment and decreased by 22% at 12 and 24 hours. In liver, PFOA is also the major metabolite reaching peak concentrations (38-44 ng/g) at 12 hours post-treatment. The highest concentration of perfluorononanoic acid (PFNA) coincides with peak PFOA concentrations and both metabolites decreased at 24 hours. In conclusion, the appearance of PFNA in the liver suggests that alpha-oxidation occurs although it does not appear to be the predominant metabolism pathway. However, these results suggest the telomer alcohol is metabolized by both alpha- and beta-

oxidation pathways. Analysis of the brain, kidney, spleen, gonads, and fat is ongoing.

Test substance : 8-2 Telomer alcohol (perfluorooctyl ethanol)

20.10.2005 (317)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : mouse
Number of animals
Males : 39
Females : 39
Doses
Males : 1 or 10 mg/kg
Females : 1 or 10 mg/kg
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : The present study is designed to examine the pharmacokinetic properties of PFOA in the mouse. Young male and female CD-1 mice received a single gavage administration at either 1 or 10 mg/kg. Three animals from each group were sacrificed at 4, 8, or 12 hours, or 1, 3, 6, 9, 13, 20, 27, 34, 42, or 48 days after treatment. Serum was prepared from trunk blood collected from the descending aorta and analyzed for PFOA by HPLC-MS-MS.

Result : PFOA was absorbed readily, reaching Cmax between 4-8 hours. In contrast to the rat, no discernable sex difference in the disposition of PFOA was observed in the mouse. The terminal serum half-life of PFOA was estimated in the range of 15-20 days. A similar pharmacokinetic profile was seen in both dose groups, suggesting linearity between body burden of the fluorochemical and administered doses up to 10 mg/kg. These results thus indicate a significant difference in the pharmacokinetic disposition of PFOA between the rat and the mouse, with the profile of the latter species resembling the lack of an apparent sex-dependent elimination in humans.

Test substance : PFOA

20.10.2005 (405)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males :
Females :
Doses
Males : 150 mg/kg
Females :
Vehicle :
Route of administration : i.p.
Exposure time :

Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : The metabolic fate of perfluoro-n-octanoic-acid (PFOA) and perfluoro-n-decanoic acid (PFDA) was studied in rats. Male Fischer-344-rats were injected intraperitoneally with 150 mg/kg PFOA or 50 mg/kg PFDA. Feed and water consumption and urine output were monitored for 8 days. Bile was collected from surgically isolated, cannulated bile ducts on days one and three post injection. Selected rats were killed on days three, seven, or eight. Urine, liver homogenate and subcellular fraction, blood, and bile samples were analyzed for PFOA and PFDA metabolites by fluorine-19 (F-19) nuclear magnetic resonance (NMR) spectroscopy. Rats were injected with PFOA and PFDA as before and in vivo NMR spectra were obtained on days two, three, seven, nine, ten, 13, 22, and 51. The spectra were analyzed for PFOA and PFDA metabolites.

Result : PFOA caused a significant transient decrease in food consumption. The maximum decrease occurred on day two post injection. PFDA caused a prolonged decrease in food consumption that lasted throughout the study period. Both PFOA and PFDA caused sustained decreases in water consumption. PFDA caused the greater decrease. PFDA caused a gradual decrease in urine output to around 2 mL by day five. PFOA caused a rapid transient increase in urine output that peaked at 22.3 mL during the first 24 hours. Only unchanged PFOA and PFDA were found in the body fluid and liver homogenate and subcellular fraction samples. Comparison of the signal to noise ratios of the NMR spectra indicated that PFOA was readily preferentially excreted in the urine and PFOA was transported preferentially in the bile. Signals due to inorganic fluorides were detected in the urine spectra of exposed and control rats. The fluorides were thought to originate in the feed. The in vivo liver spectra contained resonances originating from unchanged PFOA and PFDA. The authors conclude that PFOA and PFDA do not appear to be metabolized in vivo. The greater acute toxicity of PFDA relative to that of PFOA may be related to differences in the excretory processes that clear the compounds from the body.

Test substance : PFOA

15.11.2005 (284)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 2 mg of non-ionic fluorine as PFOA
Females : 2 mg of non-ionic fluorine as PFOA
Vehicle :
Route of administration : unspecified
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :

Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1982
GLP : no data
Test substance : other TS

Method : The urinary excretion was investigated male and female rats following a 2 mg dose of non-ionic fluorine as PFOA.
Result : Female rats excreted 76% of a 2 mg dose of non-ionic fluorine as PFOA in the urine in 24 hours whereas male rats excreted only 9.2% of the dose. The effect of probenecid, an inhibitor of the organic acid transport system, on these measurements was also determined. In female rats the PFOA clearance was several fold greater than the inulin clearance and the clearance of PFOA was markedly reduced by probenecid. Conversely, in male rats, the PFOA clearance was only a fraction of the inulin clearance and was virtually unaffected by probenecid. This difference in PFOA excretion by male and female rats may explain the sex-related difference in PFOA toxicity in which male rats are more susceptible to high doses than females
Test substance : PFOA
20.10.2005 (299)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males : 48
Females : 48
Doses
Males : 3, 10, or 30 mg/kg
Females : 3, 10, or 30 mg/kg
Vehicle :
Route of administration : gavage
Exposure time : 28 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1:st
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1987
GLP : no data
Test substance : other TS

Method : The aim of the present study was to compare the urinary elimination of PFOA between the two sexes during subchronic administration to the Wistar rat. PFOA was administered by gavage to 48 newly-weaned animals at 0 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg for 28 consecutive days. The urine was collected on the 7th and 28th day of the study. At the end of the study, blood was collected by cardiac puncture. At necropsy, tissue specimens for histopathologic examination were collected from the controls and from the group receiving 30 mg/kg of PFOA daily.
Result : Unlike the female rats, on the 7th day of the study all three groups of male rats excreted significant less PFOA than their daily dose of PFOA, which suggested that the males had not reached a steady state by seven days.

On the 28th day, the males excreted an amount of PFOA equal to their daily dose. The PFOA concentrations in the plasma of the male animals suggested that the binding sites of PFOA may become saturated at the chronic daily dose level of 30 mg/kg.

Test substance : PFOA

02.12.2005 (301)

In Vitro/in vivo : In vivo
Type : Excretion
Species : dog
Number of animals
Males : 5
Females : 5
Doses
Males : 30 mg/kg
Females : 30 mg/kg
:

Route of administration : i.v.
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests :
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1988
GLP : no data
Test substance : other TS

Method : The excretion kinetics of PFOA were investigated in the beagle dog. Six laboratory bred beagle dogs (3 male, 3 female) were anesthetized with methoxyflurane and catheters were placed in both ureters after laparototomy and cystotomy. The animals were given an intravenous dose of 30 mg/kg of PFOA followed by continuous infusion with 5% mannitol solution at 1.7 mL/min. Urine was collected at 10 minute intervals for 60 minutes. A 5 mL blood sample was collected in the middle of each urine sampling period. Probenicid (30 mg/kg i.v.) was then administered, and urine and blood samples were again collected as before. Renal clearance of PFOA was calculated for the before and after probenecid injection periods. Four additional dogs (2 male, 2 female) were given 30 mg/kg PFOA intravenously. These dogs were kept in metabolism cages, and blood samples were collected intermittently for 30 days. From these dogs, plasma PFOA half-lives were determined.

Result : Renal clearance rate was approximately 0.03 mL/min/kg. Probenecid significantly reduced the PFOA clearance in both sexes, indicating an active secretion mechanism for PFOA. The plasma half-lives of PFOA were longer in the male dogs (473 and 541 hours) than in the female dogs (202 and 305 hours).

Test substance : PFOA

20.10.2005 (300)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males : 40
Females : 20
Doses
Males : 5, 25, and 125 mg/kg

Females : 5, 25, and 125 mg/kg
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1:st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : Groups of 10 male and 5 female rats were each dosed daily by gavage with either 0 (control), 5, 25, or 125 mg 8-2 Telomer B Alcohol/kg/day. A number of toxicology end-points, such as body weights, liver and kidney weights were recorded during and at the end of the study. Blood samples were analyzed for total fluorine levels weekly.
Result : Steady-state concentrations were reached between test days 60 and 84. At steady-state, pooled plasma samples obtained from males and females over the duration of the study were analyzed for 8-2 Telomer B Alcohol (parent compound), 8-2 Telomer B acid, perfluorooctanoate acid (PFOA), perfluorononanoic acid (PFNA), and total fluorine levels. The level of parent compound detected did not exceed 0.074 ppm in either males or females. In males, PFOA represented approximately 85% of the total plasma fluorine. In females, PFOA represented approximately 5%. The 8-2 acid of Telomer B Alcohol and PFNA were also found in plasma of both males and females. Significantly lower mean body weights and increased liver weights compared to control were observed in male rats administered 125 mg/kg/day.
Test substance : 8-2 Telomer B Alcohol (perfluorooctyl ethanol)
01.11.2005 (375)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 20 mg/kg
Females : 20 mg/kg
Vehicle : other: propylene glycol/water (1:1)
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1:st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2001
GLP : no data
Test substance : other TS

Method : Male and female Wistar rats of 5 weeks old were used in this study. After acclimatization for 1 week, rats were intraperitoneally administered with PFHA, PFOA, PFNA or PFDA that were dissolved into propylene glycol: water (1:1, v:v) at a dose of 20 mg/ml/kg body weight. Rats were individually placed in metabolic cages, and urine and feces were collected every 12 h up to 5 days. Some of male rats were castrated at 3 weeks old, and 2 weeks after the castration, the castrated rats were subcutaneously injected with testosterone propionate with corn oil as a vehicle (1 ml/kg body weight) at doses as indicated once a day for 4 days. Female rats of 6 weeks old were treated with testosterone propionate as described above. These rats were intraperitoneally administered with PFOA 24 h after the final treatment of testosterone, and urine samples were collected for 24 h in metabolic cages. For the collection of bile, the common bile duct was cannulated with PE10 tubing under anesthesia with Nembutal. Rats were then intravenously injected with PFHA, PFOA, PHNA or PFDA that were dissolved in serum (2 ml/kg body weight) obtained from rats of the same sex at a dose of 25 mg/kg body weight and placed in Bollman gauges. Bile samples were collected every 30 min up to 5 h after the injection, weighed, and the amounts of PFCA were determined. To compare the rate of urinary excretion rates of various PFCAs, rats were anesthetized by intraperitoneal injection of 25% (w:v) solution of urethane, and femoral vein was cannulated with SP45 tubing. Then rats were placed in Bollman gauges and continuously infused with 10% (w:v) mannitol in 0.9% (w:v) NaCl at a rate of 0.1 ml:min during experiments. Two hours after starting infusion, rats were intravenously injected with PFHA, PFOA, PHNA or PFDA dissolved in serum as described above at a dose of 25 mg/kg body weight. Urine samples were collected every 10 min (1.0-2.0 ml of urine).

Result : In male rats, perfluoroheptanoic acid (PFHA) was rapidly eliminated in urine with the proportion of 92% of the dose being eliminated within 120 hours after an intraperitoneal injection. PFOA, perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) was eliminated in urine with the proportions of 55, 2.0 and 0.2% of the dose, respectively. By contrast, four perfluorinated fatty acids (PFCAs) were eliminated in feces with the proportion of less than 5% of the dose within 120 hours after an injection. In female rats, the proportions of PFOA and PFNA eliminated in urine within 120 hours were 80% and 51% of the dose, respectively, which were significantly higher compared with those in male rats. There was the tendency that PFCA with longer carbon chain length is less eliminated in urine in both male and female rats. Fecal elimination of PFCAs was not different between PFCAs in female rats and comparable to those in male rats. The rates of biliary excretion of PFCAs in male rats were slower than those in female rats. Sex-related difference in urinary elimination of PFOA was abolished when male rats had been castrated. On the contrary, treatment with testosterone suppressed the elimination of PFOA in urine in both castrated male rats and female rats. The effect of testosterone was in a time- and dose-dependent manner. These results suggest that PFCAs are distinguished by their carbon chain length by a renal excretion system, which is regulated by testosterone.

Test substance : PFOA

02.12.2005 (397)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 9.4 umol/kg (3.9 mg/kg)
Females : 9.4 umol/kg (3.9 mg/kg)
Vehicle :
Route of administration : i.p.

Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2.nd :
3.rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : Urinary excretion of PFOA is more rapid in female than male rats but the reason is unknown. Our objectives were to (1) compare elimination, tissue distribution, and metabolic fate of PFOA in the 2 sexes and (2) determine if PFOA is incorporated into triacylglycerols, cholesteryl esters, or phospholipids as a PFOA-containing hybrid lipid. Male and female rats were administered PFOA by intraperitoneal injection and the urine, feces, bile collected for analysis. After sacrifice, major organs were collected and analyzed for PFOA.

Result : The t1/2 for whole body elimination of [1-14C]PFOA (9.4 umol/kg, ip) was less than one day in females compared to 15 days in males. Females eliminated PFOA rapidly in urine (90% of the dose in one day) whereas males eliminated it slowly and to a similar extent in urine and feces (35% of dose by each route in 28 days). Fecal elimination was due in part to biliary excretion of PFOA. HPLC analysis of bile and urine extracts from females and males indicated that only the parent compound was excreted. Major tissues of distribution in both sexes were the liver and blood followed by the kidney. Analysis of plasma and tissue extracts showed that only the parent compound was present. This indicates that a PFOA-containing hybrid lipid is not formed in either sex, PFOA is less persistent in females because the parent compound is cleared more rapidly by renal excretion. Castration of males greatly increased the elimination of PFOA into both urine and feces, but castration plus estradiol produced no further augmentation. In female rats, neither ovariectomy nor ovariectomy plus testosterone affected the elimination of PFOA concluding that a factor produced by the testis, most likely androgens, modulate the elimination of PFOA in the male rat.

Test substance : PFOA

06.12.2005 (146) (402)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : Plasma time-concentration profiles of PFHA, PFOA, PFNA and PFDA were determined after an intravenous injection in male and female rats. Toxicokinetic parameters were calculated from plasma time-concentration profiles.

Result : Toxicokinetics were compared between perfluoroheptanoic acid (PFHA), PFOA, perfluorononanoic acid (PFNA) and PFDA in male and female rats. Plasma half lives (t1/2) in male and female rats were calculated to be 0.10 and 0.05 days, respectively, for PFHA, 5.63 and 0.08 days for PFOA, 29.5 and 2.44 days for PFNA and 39.9 and 58.6 days for PFDA. Total plasma clearance (CLtot) of PFHA was higher than those of other perfluorocarboxylic acids (PFCAs) in both male and female rats. By contrast, CLtot of PFDA was extremely low in both sexes. PFCAs having shorter carbon chain length showed higher CLtot. There was a significant sex-related difference in CLtot of PFOA and PFNA. Distribution volumes in steady state (Vss) were not much different between PFCAs and between sexes. To estimate the role of urinary excretion in plasma clearance of PFCA, renal clearance (CLR) was determined for PFCAs. CLR of PFCAs were in the order PFHA > PFOA > PFNA~PFDA and PFHA~PFOA > PDNA > PFDA in male and female rats, respectively. There was a close relationship between CLtot and CLR. Plasma protein binding, estimated in vitro, was over 98% for all PFCAs tested. The results indicate that CLR is responsible for the difference in CLtot between PFCAs having different carbon chain length and between sexes.

Test substance : PFOA

06.12.2005 (463)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : monkey
Number of animals
Males : 3
Females : 3
Doses
Males : 10 mg/kg
Females : 10 mg/kg
:

Route of administration : i.v.
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : The pharmacokinetics and urinary excretion of perfluorooctanoate were investigated in male and female cynomolgus monkeys. Three male and 3 female monkeys were administered a single iv bolus dose of 10 mg/kg of potassium perfluorooctanoate. At 0.5 hours after dosing, serum concentrations of perfluorooctanoate were determined. Serial serum measurements were made through 123 days after dosing. Urine measurements of perfluorooctanoate were made for 28 days after dosing.

Result : At 0.5 hours after dosing, serum concentrations of perfluorooctanoate were similar in male and female monkeys and ranged from 91,130 to 96,600 ng/mL in male monkeys and from 88,940 to 96,400 ng/mL in female monkeys. Serum concentrations of perfluorooctanoate subsequently declined but, beyond the first few days after dosing, the rate of decrease appeared to be faster in male monkeys than in female monkeys. On day 28, the concentrations of perfluorooctanoate in serum ranged from 1863 to 27,140 ng/mL in the male monkeys and from 7145 to 33,680 ng/mL in the

female monkeys. On day 123 after dosing, the serum concentration of perfluorooctanoate was only slightly above the limit of quantitation (20 ng/mL) in male monkeys and between 885 and 4701 ng/mL in female monkeys. The terminal half-life of perfluorooctanoate in serum was 13.6, 13.7, and 35.3 days in the 3 male monkeys and 26.8, 29.3, and 41.7 days in the 3 female monkeys. The total body clearance was 4.0, 15.8, and 17.5 mL/day/kg for the 3 male monkeys and 3.1, 3.9, and 9.1 mL/day/kg for the 3 female monkeys. The volume of distribution of perfluorooctanoate was similar for both sexes and ranged from 168 to 192 mL/kg for male monkeys and 133 to 270 mL/kg for female monkeys. Perfluorooctanoate was slowly excreted in the urine by both male and female monkeys; levels of perfluorooctanoate, representing as much as 1% of the administered dose, were present in urine 28 days after dosing.

Test substance : Potassium salt of PFOA

16.11.2005 (24)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 4 mg/kg
Females : 4 mg/kg
Vehicle :
Route of administration : i.p.
Exposure time : 28 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : The elimination, tissue distribution, and metabolism of radiolabeled PFOA was examined in male and female rats for 28 days after a single ip dose of 4 mg/kg.

Result : A sex difference in urinary elimination of PFOA-derived 14C was observed. Female rats eliminated PFOA-derived radioactivity rapidly in the urine with 91% of the dose being excreted in the first 24 hours. In the same period, male rats eliminated only 6% of the administered 14C in the urine. The sex-related difference in urinary elimination resulted in the observed difference in the whole-body elimination half-life (t1/2) of PFOA in males (t1/2 = 15 days) and females (t1/2 less than 1 day). Analysis of PFOA-derived 14C in tissues showed that the liver and plasma of male rats and the liver, plasma, and kidney of female rats were the primary tissues of distribution. The relatively high concentration of PFOA in the male liver was further examined using an in situ non-recirculating liver perfusion technique. It was shown that 11% of the PFOA infused was extracted by the liver in a single pass. The ability of the liver to eliminate PFOA into bile was examined in rats whose renal pedicles were ligated to alleviate sex differences in the urinary excretion of PFOA. In a 6-hour period following IP administration of PFOA, there was no apparent difference in biliary excretion, where both males and females eliminated less than 1% of the PFOA dose via this route. It was hypothesized that the sex difference in the persistence of

PFOA was due to a more rapid formation of a PFOA-containing lipid (i.e., a PFOA-containing mono-, di-, or triacylglycerol, cholesteryl ester, methyl ester, or phospholipid) in the male rat. Also, the increased urinary elimination of PFOA in females may have been due to increased metabolism to a PFOA-glucuronide or sulfate ester. However, no evidence that PFOA is conjugated to form a persistent hybrid lipid was obtained, nor were polar metabolites of PFOA in urine or bile detected. In addition, daily urinary excretion of fluoride in male and female rats before or after PFOA treatment were similar, suggesting that the parent compound is not defluorinated. Thus, the more rapid elimination of PFOA from female rats is not due to formation of a PFOA metabolite.

Test substance : PFOA

06.12.2005 (614)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 4 mg/kg
Females : 4 mg/kg
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : There is a marked sex difference in the whole-body elimination of PFOA in rats, with females excreting the perfluorinated acid much more rapidly than males. The objective of this study was to determine if androgens or estrogens are involved in causing this sex difference in PFOA elimination. Urinary excretion was determined following castration of males and ovariectomy or ovariectomy plus testosterone in females.

Result : Castration of males greatly increased the elimination of [1-14C]PFOA (4 mg/kg, i.p.) in urine, demonstrating that a factor produced by the testis was responsible for the slow elimination of PFOA in male rats. Castration plus 17beta-estradiol had no further effect on PFOA elimination whereas castration plus testosterone replacement at the physiologic level reduced PFOA elimination to the same level as rats with intact testes. Thus, in male rats, testosterone exerts an inhibitory effect on renal excretion of PFOA. In female rats, neither ovariectomy nor ovariectomy plus testosterone affected the PFOA urinary elimination, demonstrating that the inhibitory effect of testosterone on PFOA renal excretion is a male-specific response. Probenecid decreased the high rate of PFOA renal excretion in castrated males but had no effect on male rats with intact testes. We conclude that testosterone is a key determinant of the sex difference in PFOA elimination in rats.

Test substance : PFOA

06.12.2005 (610)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 50 mg/kg
Females : 50 mg/kg
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1989
GLP : no data
Test substance : other TS

Method : The urinary excretion of PFOA was studied in male Wistar rats after castration and estradiol administration as well as in intact females and males. The rats were administered as a single intraperitoneal dose of 50 mg/kg of PFOA.

Result : During the first 24 hours females excreted 72 +/- 5% (N = 6) of a single intraperitoneal dose of PFOA in urine whereas the intact males excreted only 9 +/- 4% (N = 6). After castration followed by estradiol administration (500 ug/kg every 2nd day for 14 days), the males excreted PFOA in urine in similar amounts as the females (68 +/- 14% at 24 hr, N = 10). Estradiol treatment of non-castrated males produced similar results (61 +/- 19% at 24 hours, N = 10). Also castration without estradiol administration significantly enhanced the renal PFOA excretion, but not as effectively as estradiol treatment. After 96 hours, the concentration of PFOA in serum of intact males was 17-40 times higher than in the serum of other groups. PFOA was similarly bound by the proteins in the serum of females and males. Phase II metabolism of PFOA was not shown either in males or females.

Test substance : PFOA

06.12.2005 (648)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males :
Females :
Doses
Males : 50 mg/kg
Females : 50 mg/kg
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :

3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1990
GLP : no data
Test substance : other TS

Method : The distribution and accumulation of PFOA, following exposure to rats, was determined. Adult Wistar rats were administered PFOA as a single intraperitoneal dose of 50 mg/kg. Newly weaned rats were administered daily gavage doses of 3, 10, or 30 mg/kg for 28 days. Differences in the distribution and accumulation of PFOA were determined. Samples taken for analysis included brain, liver, kidney, lung, spleen, ovary, testis, and adipose tissues, along with a blood sample. Following the 50 mg/kg dose, samples were taken at 12 to 336 hours. For the 3, 10 and 30 mg/kg per day doses, samples were taken on the final day. The analyses were performed by GC and GC/mass spectrometry.

Result : Results from single exposures demonstrated that serum and various tissue levels of PFOA were higher in males than females. Twelve hours after PFOA dosage the serum level in females was 10 percent, while males showed a serum level of 40 percent. The biological half lives of PFOA were 24 and 105 hours for females and males, respectively. The 28-day exposures also showed that serum PFOA concentrations were higher in males for all doses. Although either single or multiple doses of PFOA resulted in the serum having the highest PFOA levels, the liver, kidneys, and lung also exhibited significant amounts of PFOA.

Test substance : PFOA

06.12.2005 (650)

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males :
Females :
Doses
Males : 150 mg/kg
Females :
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1998
GLP : no data
Test substance : other TS

Method : PFOA, PFDA, clofibrate, di(2-ethylhexyl)phthalate (DEHP), and Wy-14,643 represent a class of compounds known as peroxisome proliferators (PPs). Such compounds induce biogenesis of liver peroxisomes and cause a varying degree of hepatotoxicity and carcinogenesis in rodents. The effects of these PPs on rat hepatic lipids and phospholipid profiles were examined using phosphorus-31 NMR spectroscopy.

Male Fischer-344 rats were paired according to similar body weights for treatment and control groups. Body weights and food consumption were monitored daily, and control animals were given the same amount of food that paired partners had consumed on the previous day (pair-fed controls). Pair-feeding simulates hypophagic effects which are associated with treatments, particularly PFDA. All rats in treatment and pair-fed control groups were fasted 12-17 h prior to experiments involving liver lipid analyses. PFOA and PFDA were delivered in propylene glycol/H2O (1:1, v/v) via a single ip injection (150 mg/kg PFOA; 50 mg/kg PFDA). Procedures involving lipid extraction from rat livers were initiated at 3 days post-treatment with PFOA and at 12, 24, 48, and 120 h (5 days) post-treatment with PFDA. Clofibrate was mixed in 0.9% saline and administered as an ip injection once daily for three consecutive days (250 mg/kg/day). Experiments involving clofibrate-treated rats were initiated 4 days post-initial-treatment (i.e., 2 days after the final dose). DEHP was given as the neat oil, and Wy-14,643 was dissolved in olive oil. A single dose (1200 mg/kg for DEHP or 250 mg/kg for Wy-14,643) was administered via gastric intubation once daily for 3 consecutive days. Experiments involving treatments with DEHP or Wy-14,643 were initiated 3 days post-initial-treatment (i.e., 1 day after the final dose).

Result : All the PPs caused a 25-57% increase in hepatic phospholipid content, while all but clofibrate increased the total lipid content by 26-156%. Treatments also influenced the composition of liver phospholipids. Phosphatidylcholine (PtdCho) and phosphatidylethanolamine (PtdEth) contents were significantly increased in all treatment groups. Most notably, PFDA caused the largest increase in PtdCho and PtdEth content (about 70%), while PFOA and Wy-14,643 were the only test compounds that influenced the PtdCho:PtdEth ratio. PFDA also caused a 30% decrease in sphingomyelin (SphM) from 24 to 120 hours post-dose. SphM is a key lipid in signal transduction processes involved in apoptosis. Hydrolysis of SphM can be mediated through the action of tumor necrosis factor (TNF-alpha). The TNF-alpha concentrations in rat sera at 24 hours post-PFDA-exposure showed an 8-fold increase relative to vehicle-treated controls. These data demonstrate that an increase in the serum TNF-alpha level correlates with the time frame for the observed reduction in hepatic SphM. PFOA, a structurally similar compound, had no effect on hepatic SphM content, nor did it affect the serum TNF-alpha concentration. These effects may be related to differences in the tumorigenicity associated with these compounds. It is postulated that PFDA activates the SphM signal transduction pathway via the release of TNF-alpha. This then stimulates cytotoxic responses and processes of apoptosis and may suppress cell proliferative and mitogenic responses.

Test substance : PFOA

06.12.2005 (68)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males : 25 mg/kg
Females : 25 mg/kg
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :

3rd:

Toxic behaviour :
Deg. product :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : The protein binding properties of PFOA were investigated in rat liver, kidney and plasma. The binding properties between PFOA and human serum albumin were also obtained.

Result : Most PFOA was in protein-bound form in plasma, and the primary PFOA binding protein in plasma was serum albumin. The dissociation constants for binding of PFOA to rat serum albumin or human serum albumin and the numbers of PFOA binding sites were in the range of 0.3 to 0.4 mM and 6 to 9, respectively.

There is no sex related difference in PFOA plasma protein binding. Therefore, binding to albumin in plasma will not be a determining factor in PFOA elimination in rats.

Based on the low binding affinity between PFOA and serum albumin, fatty acid displacement by PFOA in vivo would be very unlikely.

alpha2u-Globulin is a male rat specific protein that can be freely filtered by the glomerulus. The binding between PFOA and alpha2u-globulin is rather weak. The dissociation constant is in the magnitude of 10-3 M. This weak binding would not induce adequate reabsorption of PFOA in kidney, to the extent necessary to account for the slow elimination of PFOA in male rats. It is also noted that alpha2u belongs to a superfamily of low molecular weight proteins that are capable of binding small lipophilic molecules.

Significant amounts of PFOA bind to cytosolic proteins in rat liver and kidney. However, only in the kidney cytosol does the percentage of protein bound PFOA appear to be higher in the male rats than in the female rats.

Based on the ligand blotting results, PFOA is able to bind to various rat liver proteins, but the binding does not seem to be sex dependent.

In summary, the protein binding properties of PFOA in rat liver, kidney and plasma were studied. There is no evidence of sex-related protein binding that could rationally explain the sex-dependent PFOA elimination in rats. The binding properties between PFOA and human serum albumin were also obtained. Available evidence suggests that their binding is not responsible for the apparent long half of PFOA in human plasma.

Test substance : PFOA

06.12.2005 (222) (296) (297)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : After a single intravenous dose of [14C]APFO or of potassium [14C]perfluorooctanesulfonate, rats were administered cholestyramine as a 4% mixture in feed for 14 or 21 days, respectively.

Result : After a single intravenous dose of [14C]APFO [14C]PFO, 13.3 mg/kg) or of potassium [14C]perfluorooctanesulfonate [(14C]PFOS, 3.4 mg/kg) to rats, cholestyramine fed daily as a 4% mixture in feed was shown to increase the total carbon-14 eliminated via feces and to decrease liver concentration of carbon-14. Rats were fed cholestyramine in feed for 14 days after administration of [14C]PFO and for 21 days after administration of [14C]PFOS. Control rats were administered radiolabeled fluorochemical but were not treated with cholestyramine. Cholestyramine treatment increased mean cumulative carbon-14 elimination in feces by 9.8-fold for rats administered [14C]PFO and by 9.5-fold for rats administered [14C]PFOS. After [14C]PFO, a mean of 4% of the dose of carbon-14 was in liver of cholestyramine-treated rats at 14 days versus 7.6% in control rats; after [14C]PFOS, 11.3% of the dose was in liver at 21 days versus 40.3% in control rats. After administration of either radiolabeled compound, plasma and red blood cell carbon-14 concentrations, which were relatively lower than liver concentrations, were also significantly reduced by cholestyramine treatment.

06.12.2005 (342)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rabbit
Number of animals
Males :
Females : 5
Doses
Males :
Females : 0, 4, 16, 24, or 40 mg/kg
:
Route of administration : i.v.
Vehicle :
:
Exposure time :
Decision on results on acute tox. tests
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1:st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1995
GLP : yes
Test substance : other TS

Method : APFO was administered by i.v. injection to rabbits and blood samples taken at 2, 4, 6, 8, 12, 24, and 48 hours post dose.

Result : The total organic fluorine for whole liver for control animals, and animals administered 4, 16, or 24 mg/kg i.v. doses of a 45% solution of APFO are 20 ug, 43 ug, 66 ug, and 54 ug, respectively. An animal dosed with 40 mg/kg died 5 minutes after injection. Serum concentrations decrease rapidly with time and are non-detectable at 48 hours. The biological half-life appears to be about 4 hours.

Test substance : 45% PFOA tetrabutylammonium salt in water and isopropyl alcohol.

16.11.2005 (61) (315)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rabbit

Number of animals
Males : 18
Females : 18
Doses
Males : 0, 4, 16, or 40 mg/kg
Females : 0, 4, 16, or 40 mg/kg
: water
Route of administration : dermal
Vehicle : 24 hour(s)
:
Exposure time :
Decision on results on acute tox. tests :
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1995
GLP : yes
Test substance : other TS

Method : Groups of 3 male and 3 female rabbits were dermally administered 0, 4, 16, or 40 mg/kg of the test material and the treatment sites occluded for a 24-hour exposure period. Blood samples were taken 24-hours post-dose and on days 4, 8, 15, and 22. In addition, livers, bile, dermal application sites, and kidneys were collected for PFOA analysis.
Result : All total organic fluorine concentrations were below the practical quantitation limit. Serum levels were also below the practical quantitation limits of the analysis at day 1 and 2 after administration of the test material.
Test substance : 45% PFOA tetrabutylammonium salt in water/isopropyl alcohol.
16.11.2005 (60) (316)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males : 30
Females :
Doses
Males : 400 mg/kg
Females :
Vehicle :
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 1981
GLP : no data
Test substance : other TS

Method : A gas chromatographic technique utilizing a microwave-sustained helium plasma detector (GC/MPD) was developed to study the biotransformation of IH,IH,2H,2H-perfluorodecanol in adult male rats. The metabolic products resulting from a single oral dose of the alcohol were isolated from the blood

plasma by an extraction technique, derivatized, and characterized by the GC/MPD system with confirmation by fluorine NMR.

Result : Four fluorine-containing metabolites were detected by the fluorine-specific channel of the element-selective MPD and one of these was shown to be perfluorooctanoate. Appearance of perfluorooctanoate as a metabolite and an additional observation of concomitant elevation in plasma and urinary inorganic fluoride suggests that the biotransformation of the above alcohol to the perfluorooctanoate involves defluorination of the CF2 group adjacent to the CH2, group in the parent compound.

Test substance : Telomer 8-2 alcohol (IH,IH,2H,2H-perfluorodecanol).

08.11.2005 (293)

In Vitro/in vivo : In vitro
Type : Toxicokinetics
Species :
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : The basis for constructing and validating a human PBPK model for PFOA are described and evaluated.

Result : PFOA is a surfactant, which has received significant interest in recent years due to its reported prevalence in blood samples from many US citizens. Consequently, there has been some activity associated with constructing a human PBPK model to relate inhalation and oral exposures to PFOA levels in plasma. While there have been many kinetic studies conducted on rodents, the rodent kinetic data have not been useful in extrapolation to PFOA kinetics in humans. There are several considerations relevant to the construction of a human PBPK model that will determine how, or even if, such a model is appropriate for PFOA. First, PFOA is a surface-active chemical, which will affect its behavior in biological systems and has thus far complicated any efforts to determine tissue to blood partition coefficients. Second, PFOA is reported to be unmetabolized in mammalian systems, thereby eliminating the need for explicit description of metabolizing organs or tissues. Third, the elimination rate is dramatically different between humans and rodents. The reported half-life in humans is approximately 4 years as compared to 2 hours in the female rat. Further, rats have sex dependent elimination rates, which do not appear to be relevant to humans. Fourth, controlled human exposures to PFOA are lacking; therefore, any attempts to validate a PBPK model would be severely limited. This is further complicated by the fact that elimination mechanisms have not been completely elucidated in rats and humans. These considerations and gaps in the understanding of species-specific elimination of PFOA make it impractical to construct and apply a human PBPK or generic kinetic model to predict PFOA concentrations in plasma following ingestion or inhalation of PFOA.

Test substance : PFOA

06.12.2005 (495)

In Vitro/in vivo : In vitro
Type : Metabolism
Species :
Number of animals
Males :

Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : Fluorotelomer alcohols [FTOHs] are a novel class of polyfluorinated contaminants, recently detected in the North American atmosphere, that are possible precursors to the series of perfluoroalkyl carboxylates (PFCAs) in human blood. An in vivo rat study validated earlier independent work that poly- and perfluoroalkyl carboxylates were metabolites of FTOHs, but detection of several novel metabolites prompted examination of their pathways in greater detail using isolated rat hepatocytes. Using 8:2 FTOH as a model compound, the metabolic products formed by isolated rat hepatocytes were identified, and three synthesized intermediates were incubated separately to elucidate the metabolic pathways.

Result : For 8:2 FTOH, a major fate was direct conjugation to form the O-glucuronide and O-sulfate. Using 2,4-dinitrophenylhydrazine (DNPH) trapping, the immediate oxidation product of 8:2 FTOH was identified as 8:2 fluorotelomer aldehyde (8:2 FTAL). 8:2 FTAL was transient and eliminated HF non-enzymatically to yield 8:2 fluorotelomer alpha,beta-unsaturated aldehyde (8:2 FTUAL) which was also short-lived and reacted with GSH and perhaps other endogenous nucleophiles. Four polyfluorinated acid intermediates were also detected, including 8:2 fluorotelomer carboxylate (8:2 FTCA), 8:2 fluorotelomer alpha,beta-unsaturated carboxylate (8:2 FTUCA), tetrahydroperfluorodecanoate, and dihydroperfluorodecenoate. 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. The fate of the unsaturated metabolites, 8:2 FTUAL and FTUCA, included conjugation with GSH and dehydrofluorination to yield alpha,beta-unsaturated GSH conjugates, and GS-8:2 FTUAL which was subsequently reduced to the corresponding alcohol. PFOA and minor amounts of perfluorononanoate (PFNA) were confirmed as metabolites of 8:2 FTOH, and the respective roles of beta- and alpha-oxidation mechanisms are discussed. Preincubation with aminobenzotriazole, but not pyrazole, inhibited the formation of metabolites, suggesting that their oxidation was catalyzed by P450, not alcohol dehydrogenase.

Test substance : 8:2 Telomer alcohol (1H,1H,2H,2H-perfluoro-1-decanol)

06.12.2005 (428)

In Vitro/in vivo	:	In vitro
Type	:	Metabolism
Species	:	
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : Perfluorooctanoic acid (PFOA) is a fluorinated fatty acid analogue used as a surfactant in the manufacture of fluoropolymers. Previous studies have

indicated that PFOA was metabolically inert in mammals, but recent metabolism studies with related fluorochemicals suggested that PFOA might form a glucuronide conjugate. 14C-PFOA was incubated with male and female human and rat liver, kidney, and small intestine microsomes. Incubations were carried out in the presence of alamethicin and beta-saccharolactone to increase access of PFOA to the enzyme active site and to inhibit potential hydrolysis of PFOA-glucuronide by microsomal beta-glucuronidase, respectively.

Result : Although positive control experiments using p-nitrophenol demonstrated significant UDP-glucuronosyltransferase (UDPGT) activity in all of the tested microsomal preparations, no evidence for formation of a PFOA-glucuronide was obtained, either by high-sensitivity radiochromatography or by LC/MS. These data suggest that PFOA is not a substrate for human or rodent microsomal UDPGTs.

Test substance : PFOA

08.11.2005 (370)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males : 3
Females :
Doses
Males : 11.4 mg/kg
Females :
Vehicle : physiol. saline
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other: Absorption of APFO in rats after a single oral dose
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Male Charles River CD rats, 10 weeks old, were conditioned to individual metal metabolism cages for 24 hours prior to dosing. Each non-fasted rat was weighed immediately before being given a single oral dose of 14C-labeled APFO as a solution in 0.9% NaCl solution. The average APFO dose was 11.4 mg/kg. Groups of 3 rats were sacrificed at 1, 2, 6, 12, 24, 48, 96, and 144 hours post-dose. Blood was immediately drawn from these rats. In addition to plasma, and red blood cells, total urine and feces, spleen, digestive tract plus contents (esophagus, stomach, small intestine, large intestine, and colon), and the remainder of the carcass were saved from each of the 3 rats in the 24 and 48 hours post-dose groups for carbon-14 analysis.

Result : After a single oral dose of 14C-PFOA (mean dose, 11.0 mg/kg) in solution to groups of three male rats, at least 93% of the total carbon-14 was absorbed at 24 hours. The half-life for elimination of total carbon-14 from plasma is 4.8 days.

02.12.2005 (516)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat

Number of animals
Males :
:
Doses
Females :
: 2 mg
Males : water
Females
Route of administration : gavage
Vehicle
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: Serum levels of PFOA following oral administration
Year : 1980
GLP : no data
Test substance : other TS

Method : The metabolic fate of PFOA was determined by administration by gavage to a group of female rats. Urine and feces were collected and the PFOA content was determined.
Result : In female rats, an average of 749 ug or 37% of the fluorine in the administered dose was recovered in the urine within 4.5 hours after PFOA dose [by stomach intubation 2 mL of an aqueous solution containing 2 mg PFOA]. The quantity of nonionic fluorine recovered in the urine increased to 61% of the dose at 8 hours, 76% at 24 hours, and 89% at 96 hours. Ionic fluoride and total fluorine was measured in the serum of the female rats. Serum from rats 4.5 hours after the administration of PFOA had a non-ionic fluorine level 13.6 ppm and virtually all of this was bound to components in the serum and not ultra-filterable. Despite the large increase in non-ionic fluorine in the serum, the ionic fluoride level remained very low (0.03 ppm). Prior to intubation of PFOA, the ionic and non-ionic fluorine levels in serum were 0.032 and 0.07 ppm, respectively. The non-ionic fluorine level in the serum decreased to 11.2 ppm at 8 hours, 0.35 ppm at 24 hours, and 0.08 ppm at 96 hours. The authors conclude that PFOA is rapidly absorbed from the gastrointestinal tract and rapidly cleared from the serum.
Test substance : PFOA
02.12.2005 (489)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males : 50
Females : 50
Doses
Males : 10 mg/kg
Females : 10 mg/kg
Vehicle : water
Route of administration : gavage
Exposure time : 24 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:

Toxic behaviour :
Deg. product :
Method : other: Plasma concentrations of PFOA in rats following the oral administration of APFO
Year : 2003
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The relationship between age and plasma concentration of PFOA in rats was investigated. Groups of 10 male and 10 female Crl:CD rats between 4 and 8 weeks old were administered 10 mg/kg of APFO in water by single oral gavage. The rats were sacrificed 24 hours later and whole blood samples were collected by cardiac puncture. The plasma concentration at 24 hours was measured by LC/MS.
Result : The results show that the plasma concentration of PFOA in rats was dependent on the age and sex of the rats.

Age Effect

In both male and female rats, the greatest age-related difference in PFOA plasma concentration was observed between 4 and 5 weeks of age. The 5-week old male rats had plasma concentrations that were 5.4-fold higher than the 4-week old male rats. In contrast, the PFOA plasma concentrations in the 5-week old female rats were 2.4-fold lower than the 4-week old female rats. PFOA levels in plasma were no longer significantly affected by age in rats of either sex that were older than 5 weeks (through study termination at 8 weeks).

Sex Comparison

At 4 weeks of age, male rats had PFOA plasma concentrations that were 2.7-fold higher than in females. The PFOA plasma concentrations in 5- to 8-week old male rats were 34.7- to 65.1-fold higher than in the females of the same age.

02.12.2005 (220)

In Vitro/in vivo : In vivo
Type : Absorption
Species : rat
Number of animals
Males :
Females :
Doses
Males : 10 and 30 mg/kg
Females : 10 and 30 mg/kg
Vehicle : water
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: Age effect on plasma concentration in post-weaning rats
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : PFOA plasma concentrations were measured in immature (3, 4, or 5 weeks

of age) rats following oral gavage doses of 10 and 30 mg/kg of APFO.

Result : Plasma concentrations varied significantly between experiments, especially when compared to a prior study with 4-week old animals. In this study, PFOA plasma concentrations are relatively constant in male rats across age groups, varying only with dose level. Female rat plasma concentrations decreased with increasing age, but was only statistically significantly at the 30 mg/kg dose level. PFOA concentrations in the urine, while not normalized for total elimination, indicated more rapid urinary excretion in female rats at all ages. The plasma concentrations from the supplemental group (added to examine the effect of fasting on PFOA concentrations in 4-week old rats), however, are significantly different from the main study levels for both male and female rats. The plasma concentration variability in 4-week old rats suggests an unknown physiological variability in animals younger than 5 weeks. As a result, the relationship between age and PFOA plasma concentration is undefined in 3-4 week old rats following oral dosing with 10 or 30 mg/kg APFO.

02.12.2005 (231)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males : 30
Females :
Doses
Males : 20 mg/kg/day
Females :
Vehicle : other: Corn oil
Route of administration : gavage
Exposure time : 10 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1.st 8.3 days
2nd :
3rd :
Toxic behaviour :
Deg. product :
Method : other
Year : 2000
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 5 male rats were administered by gavage 20 mg/kg/day of APFO for either 5 or 10 days. Approximately 2 hours after the first dose, blood was collected and total fluorine content was determined. These rats were sacrificed after 5 days and their blood and livers were collected. Additional groups of rats were administered APFO for 10 days. Groups of 5 rats were sacrificed 2 hours after the last dose or at 13, 24, 52, or 93/94 days following the last dose and their blood and livers collected.

Result : Organofluoride levels in rat blood peaked after 5 days and then decreased throughout the testing period. The Cmax was 518 ppm with a terminal half-life of 8.3 days. The accumulation index was 12.5 and the bioaccumulation index was 6497.5.

05.12.2005 (206)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males : 36
Females : 36

Doses

Males	:	3, 10, or 30 mg/kg/day
Females	:	3, 10, or 30 mg/kg/day
	:	physiol. saline

Route of administration : gavage
Vehicle : 28 day(s)
Exposure time :
Decision on results on acute tox. tests :
Product type guidance
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year : 1986
GLP : no data
Test substance : other TS

Method : PFOA was administered orally for 28 consecutive days. Another 12 animals (controls) received 0.5 mL/100 g saline each day. Animal behavior, body weight, as well as, water and food consumption were observed. Blood, urine, and some viscera were collected for the analysis of PFOA and histopathology.

Result : Serum PFOA concentrations were 6-19 times higher in the males than in the females (range 48.6-83.0 ug/mL males, and 2.4-11.2 ug/mL females). On the 7th day the mean PFOA excretion in the low dose group for the males was 157 ug/24 hours and 255 ug/24 hours for females. In the high dose group the corresponding figures were 2476 ug/24 hours (males) and 2917 ug/24 hours (females). On the 28th day the PFOA excretion for the low dose males was 609 ug/24 hours, 671 ug/24 hours for the females. In the high dose group the figures were 4619 ug/24 hours (males) and 4379 ug/24 hours (females).

Test substance : PFOA

05.12.2005 (382)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 470 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 60
Vehicle : other: Corn oil
Doses : 200, 400, 450, 500, 670, and 1000 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to 6 groups of male young adult rats. Groups of 10 male rats were administered 200, 400, 450, 500, 670, or 1000 mg/kg of the test substance. The surviving rats were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Test condition : 10 males per test group

16.11.2005 (174)

Type : LD50
Value : = 482 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : female
Number of animals : 60
Vehicle : other: Corn oil
Doses : 200, 400, 450, 500, 670, and 1000 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to 6 groups of female young adult rats. Groups of 10 female rats were administered 200, 400, 450, 500, 670, or 1000 mg/kg of the test substance. The surviving rats were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.
Test condition : 10 female rats per test group
16.11.2005 (174)

Type : LD50
Value : = 478 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 90
Vehicle : other: Corn oil
Doses : 400, 500, and 650 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Ammonium perfluorooctanoate was administered by intragastric intubation as a suspension in corn oil in single doses to 10 rats/group at concentrations of 400, 500, or 650 mg/kg. Another 30 rats, 10/group, were treated by single intraperitoneal injections with aqueous solutions of phenobarbital sodium at 80 mg/kg/day for 3 days. One day after the final treatment, the rats were administered ammonium perfluorooctanoate by intragastric intubation using the same treatment as described above. An additional group of 30 rats, 10/group, were treated with an intraperitoneal injection of aqueous solutions of proadifen hydrochloride at 50 mg/kg. One hour after this treatment, ammonium perfluorooctanoate was administered by intragastric intubation, using the same treatment as described above. The surviving rats from all treatments were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data. The phenobarbital sodium phase of the study was repeated. The rats from both phases were combined and the LD50 value was based on all 60 rats.
Result : The oral LD50 of C-8 was determined in rats pre-treated with phenobarbital sodium or proadifen hydrochloride. There were no significant differences in the LD50 value of C-8 (478 mg/kg) following pre-treatment with either phenobarbital sodium (547 mg/kg) or proadifen hydrochloride (520 mg/kg).
Test condition : 10 rats per test group
08.11.2005 (178)

Type : LD50
Value :
Species : rat
Strain : other: Crl:CD

Sex : male/female
Number of animals : 390
Vehicle : other: Corn oil
Doses :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to groups of rats. The groups (10 rats/group) were male and female newborn rats (< 2 days old), male and female weanling rats (21 days old), male and female young adults (~8-10 weeks old), and male and female older rats (age undefined). Male newborn rats were administered 130, 200, 240, 280, 330, or 370 mg/kg. Female newborn rats were administered 130, 160, 200, 220, 240, 280, or 320 mg/kg. Male weanling rats were administered 350, 400, 450, 525, 670, or 710 mg/kg. Female weanling rats were administered 350, 400, 450, or 670 mg/kg. Young adult rats were administered 350, 425, 500, or 670 mg/kg. Young adult male rat data are reported in DuPont Report No. 295-81. Older male rats were administered 200, 240, 300, 350, 400, 500, or 720 mg/kg. Older female rats were administered 225, 350, 400, 450, or 670 mg/kg. The surviving rats were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Result : C-8 was slightly toxic when administered in single oral doses to the following groups of rats: weanlings (21 days old): males, LD50 = 573 mg/kg and females, LD50 = 580 mg/kg; young adults (approximately eight to ten weeks old): males, LD50 = 470 mg/kg and females, LD50 = 453 mg/kg; older rats: males, LD50 = 336 mg/kg and females, LD50 = 343 mg/kg; newborn (less than two days old): males, LD50 = 243 mg/kg and females, LD50 = 258 mg/kg. Toxicity in regards to the sex of the rats showed no significant difference. However, newborn (less than two days old) and older rats had lower LD50 values than weanlings or young adult rats.

Test condition : 10 rats per test group

15.11.2005 (193)

Type : LD50
Value :
Species : rat
Strain : other: Crl:CD
Sex : male/female
Number of animals : 100
Vehicle : other: Corn oil
Doses : 200, 480, and 670 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : In an LD50 rangefinder test, the test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to normal male rats, castrated male rats, normal female rats, and ovariectomized female rats. Dose levels of 200, 480, and 670 mg/kg were tested in each of the test systems mentioned above (10 rats/group).

In the liver weight comparison test, 5 rats/group were administered the test substance, as a suspension in corn oil, as a single dose. Male groups were defined as male control, male 100 mg/kg, male 200 mg/kg, male castrated control, and male castrated 200 mg/kg. Female groups were defined as female control, female 100 mg/kg, female 200 mg/kg, female

ovariectomized control, and female ovariectomized 200 mg/kg. All rats were weighed and observed during a 14-day recovery period. The rats were then sacrificed and the livers were weighed.

Result : C-8 is moderately toxic when administered orally to young adult male and female rats that were normal or surgically-modified (ovarectomized or castrated). The LD50 is between 400 and 491 mg/kg of body weight. No changes in liver weight to body weight ratios were seen in female rats given single doses of up to 200 mg/kg (ovarectomized or normal). A single oral dose of either 100 or 200 mg/kg produced an increase in liver weight of male rats. Castration reduced the magnitude of the liver weight increase but rats castrated and given 200 mg/kg had heavier livers than did the controls. Clinical signs seen in C-8 treated rats included stained face and perineal area and sporadic weight loss.

Test condition : 10 rats per test group

16.11.2005 (180)

Type : LD50
Value :
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 24
Vehicle : other: Corn oil
Doses : 500 mg/kg
Method : other
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO as a suspension in corn oil was administered by gavage to 4 groups of Crl:CD young adult male rats, 6 per group at a dose level of 500 mg/kg. Three groups of these rats were intubated either before or after the APFO with 1000 mg/kg of Dowex 1-X2-Cl Ion Exchange Resin. All rats were weighed and observed over a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Result : Pre-dosing or post-dosing with Dowex 1-X2-C1 Ion Exchange Resin at 1000 mg/kg changes the toxic effects of C-8 in rats. All rats dosed with the Dowex, either before or after C-8 had reduced mortalities compared to the rats dosed with C-8 alone [5/6 deaths for C-8 alone at 500 mg/kg; 0/6 following Dowex immediately after dosing; 1/6 Dowex 2-hours before dosing; and 0/6 Dowex 2-hours after dosing].

Test condition : 6 rats per test group

25.10.2005 (182)

Type : LD50
Value : = 390 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 50
Vehicle : water
Doses : 250, 500, 1000, and 5000 mg/kg
Method : other
Year : 1987
GLP : no data
Test substance : other TS

Method : APFO as a suspension in corn oil was administered by gavage to 4 groups of Sprague-Dawley young adult male and female rats, 5 males and 5 females per group at a dose level of 250, 500, 1000, or 5000 mg/kg. All rats were weighed and observed over a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data for

each sex.

Test condition : Test groups were comprised of 5 males and 5 females
Test substance : 85% APFO, Sample T-3974, Lot 390
25.10.2005 (313)

Type : LD50
Value : = 540 mg/kg bw
Species : rat
Strain : other: Charles River CD strain
Sex : male/female
Number of animals : 50
Vehicle : other: 40% acetone and 60% corn oil
Doses : 100, 215, 464, 1000, and 2150 mg/kg
Method : other
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO as an emulsion in 40% acetone-60% corn oil was administered by gavage to groups of ChR-CD male and female rats weighing from 180-221 grams, 5 males and 5 females per group, at dose levels of 100, 215, 464, 1000, or 2150 mg/kg. All rats were weighed and observed over a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data for both sexes combined. All rats were subjected to gross necropsy shortly after death during the study or after sacrifice at 14-days post-treatment.
Test condition : Test groups were comprised of 5 males and 5 females
25.10.2005 (285) (340) (603)

Type : LD50
Value : < 500 mg/kg bw
Species : rat
Strain : other: Sherman-Wistar
Sex : male/female
Number of animals : 10
Vehicle : water
Doses : 1000 mg/kg of a 50% aqueous suspension
Method : other
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : There were 5 males and 5 females in the test group.
Result : In the 5 male rats, 2 died on day 1 and another on day 2. In the 5 female rats, 4 died on day 1. The gastric mucosa was eroded. The animals exhibited signs of writhing at times. The LD50, based on the test substance, was less than 500 mg/kg.
Test substance : The sample was dosed as a 50% w/v suspension in water.
02.12.2005 (96)

Type : LD50
Value : > 500 mg/kg bw
Species : rat
Strain : other: Crl:CD (SD) BR
Sex : male/female
Number of animals : 20
Vehicle : water
Doses : 250 and 500 mg/kg
Method : other: OECD guidelines (not specified further)
Year : 1997
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : There were 5 male and 5 female rats per test group.
Result : No mortality was observed in the 250 mg/kg group and all animals appeared normal during the study with the exception of 2 females which exhibited red-stained face and/or wet urogenital area within 24 hours of test material administration. Two males and all 5 females treated at 500 mg/kg were found dead within 4 days of test material administration. Based on the observed mortality, the estimated oral LD50 values were determined to be greater than 500 mg/kg for males and between 250 and 500 mg/kg for females.

28.10.2005 (137)

Type : LDLo
Value : = 480 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 30
Vehicle : other: Corn oil
Doses : 200, 480, and 670 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substances, ammonium perfluorooctanoate (3M) and ammonium perfluorooctanoate (Rimar Co.), as suspensions in corn oil, were administered by intragastric intubation in single doses to young adult male rats. Rats (10/group) were administered 200, 480, or 670 mg/kg of the test substance. The surviving rats were weighed and observed during a 14-day recovery period and then sacrificed.
Result : Mortality ratios of 0/10, 6/10, and 10/10 were found in the 200, 480, and 670 mg/kg ammonium perfluorooctanoate (3M) groups, respectively. Mortality ratios of 0/10, 10/10, and 10/10 were found in the 200, 480, and 670 mg/kg ammonium perfluorooctanoate (Rimar Co.) groups, respectively.

Clinical signs observed in ammonium perfluorooctanoate (3M) rats included stained and/or wet perineal area, stained face, and weight loss at all levels tested. Other clinical signs observed included weakness (480 and 670 mg/kg), diarrhea (480 mg/kg), and alopecia (200 mg/kg). All deaths occurred within 4 days after dosing.

Clinical signs observed in ammonium perfluorooctanoate (Rimar Co.) rats included stained and/or wet perineal area, stained face, and weight loss at all levels tested. Other clinical signs noted included weakness (480 and 670 mg/kg) and lethargy (670 mg/kg).

All deaths occurred within 4 days after dosing.
Test condition : 10 rats per test group

16.11.2005 (177)

Type : LDLo
Value : = 480 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 30
Vehicle : other: Corn oil
Doses : 200, 480, and 670 mg/kg
Method : other
Year : 1981

GLP : no data
Test substance : other TS

Method : Sodium perfluorooctanoate as a suspension in corn oil was administered by gavage to groups of 10 Crl-CD male rats at a dose level of 200, 480, or 670 mg/kg. All rats were weighed and observed over a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.
Result : Mortality ratios of 0/10, 4/10, and 9/10 were found in the 200, 480, and 670 mg/kg sodium perfluorooctanoate groups, respectively.

Clinical signs observed in sodium perfluorooctanoate rats included stained and/or wet perineal area and weight loss at all levels tested. Other clinical signs observed included stained face at 200 and 670 mg/kg, weakness at 480 and 670 mg/kg, and chromodacryorrhea at 200 mg/kg. All deaths occurred within 4 days after dosing.
Test condition : 10 rats per test group
Test substance : Sodium perfluorooctanoate (99+%) [CAS # 335-95-5]
02.12.2005 (177)

Type : LDLo
Value : = 670 mg/kg bw
Species : rat
Strain : other: ChR-CD
Sex : male
Number of animals : 11
Vehicle : water
Doses : 1.5, 12, 40, 120, 200, 300, 450, 670, 1000, 1500, and 2250 mg/kg
Method : other
Year : 1961
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance was administered by intragastric intubation to male rats (1 rat/group) in single doses. Concentrations tested were 1.5, 12, 40, 120, 200, 300, 450, 670, 1000, 1500, and 2250 mg/kg. Survivors were sacrificed 14-15 days later, and body weights and liver weights were recorded.
Result : APFO was administered to rats by stomach tube in single doses ranging from 1.5-2250 mg/kg. Rats administered 670 mg/kg or more, died within 18 to 43 hours after dosing. Clinical signs of toxicity were inactivity, a red discharge around the nose, perineal discoloration and weight loss. Animals receiving doses of 200 mg/kg or more showed enlarged livers.
Test condition : 1 rat per test group
02.12.2005 (157)

Type : LDLo
Value : = 670 mg/kg bw
Species : rat
Strain : other: ChR-CD
Sex : male
Number of animals : 18
Vehicle : water
Doses : 1, 1.5, 2.3, 3.4, 5.1, 26, 40, 60, 77, 90, 120, 130, 170, 200, 300, 450, 670, and 2250 mg/kg
Method : other
Year : 1968
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as an aqueous solution (pH ~6), was administered by intragastric intubation to young adult male rats (1 rat/group) in single doses. Concentrations tested were 1, 1.5, 2.3, 3.4, 5.1, 26, 40, 60, 77, 90,

120, 130, 170, 200, 300, 450, 670, and 2250 mg/kg. Survivors were sacrificed 14 days later, and body weights and liver weights were recorded.

Result : The rats administered 670 and 2250 mg/kg, died within 1 or 2 days after dosing. All the other rats survived. Rats receiving intragastric doses as low as 60-90 mg/kg had enlarged livers. Gastrointestinal irritation was also observed in rats ingesting APFO.

Test condition : 1 rat per test group

02.12.2005 (162)

Type : LDLo
Value :
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 72
Vehicle : water
Doses : 200, 480, and 670 mg/kg
Method : other
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Young adult male rats (6/group) were administered ammonium perfluorooctanoate as a 60% aqueous solution at dose levels of 200, 480, and 670 mg/kg. Additional groups of rats were pre-treated with ethanol (15% v/v) in drinking water for 14 days and then dosed with ammonium perfluorooctanoate at the same concentrations as listed above on day 15. Three other groups of rats were pretreated with a single 6000 mg/kg dose of ethanol via intragastric intubation followed 24 hours later with the ammonium perfluorooctanoate treatment at the levels listed above. An additional group of untreated rats served as controls. Groups of rats were also treated with ethanol alone at either 6000 mg/kg or 15% v/v in drinking water for 14 days. Clinical signs and body weights were recorded. Liver weights were recorded at the 14-day sacrifice.

Result : Groups of young adult rats were administered a single dose of ethanol at 6000 mg/kg or a 15% solution in their drinking water for 14 days and/or a single dose of C-8 at dose levels of 200, 480, or 670 mg/kg. In the rats administered a single dose of ethanol followed 24 hours later by C-8, all the rats administered 670 mg/kg of C-8 died within 8 days after dosing. In the rats administered ethanol for 14 days before C-8 dosing, all the rats administered 480 and 670 mg/kg of C-8 died within 6 days after dosing. Liver weight/body weight ratios showed a sharp increase in all the rats that received C-8 when compared to controls and to the rats that received only ethanol. There were no significant differences between the untreated controls and the rats that received only ethanol or between the ethanol pre-treated rats administered C-8 and the rats that received only C-8.

Test condition : 6 rats per test group

16.11.2005 (194)

Type : other: Effect of inositol trisphosphate on peroxisome proliferation
Value :
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals :
Vehicle : other: Corn oil
Doses : 150 mg/kg
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : Recent studies have shown that peroxisome proliferators cause changes in hepatic intracellular calcium concentrations. To test this, male Sprague-Dawley rats were administered 150 mg/kg of PFOA in corn oil. Peroxisomal beta-oxidation and catalase activity were measured as was modulation of hepatic inositol trisphosphate receptors, a mediator of the mobilization of calcium from intracellular stores.

Result : Recent studies have shown that peroxisome proliferators cause changes in hepatic intracellular calcium concentrations. To test this, male Sprague-Dawley rats were administered 150 mg/kg of PFOA in corn oil. PFOA-treated rats showed increased peroxisomal beta-oxidation and catalase activity by 400% and 21%, respectively, within 48 hours. In addition, hepatic inositol trisphosphate receptors, were modulated by prior treatment with PFOA. This peroxisome proliferator enhanced the affinity of these receptors (Kd was decreased by 40%), while reducing their maximal binding capacity (Bmax was reduced by 50%). These parameters returned toward control values 4 days following PFOA treatment.

Test substance : PFOA

25.10.2005 (653)

Type : other: The effect of aging on peroxisome proliferation
Value :
Species : rat
Strain : Fischer 344
Sex : male
Number of animals :
Vehicle : other: Corn oil
Doses : 150 mg/kg
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : The hepatic effects of the peroxisome proliferator PFOA were examined in 10, 20, 50, and 100 week old male Fischer 344 rats. Rats were treated by gavage with 150 mg/kg of PFOA in corn oil and sacrificed 48 hours later. Peroxisomal beta-oxidation and catalase activity were determined.

Result : The effect of aging on peroxisome proliferation was studied in 10-, 20-, 50-, and 100-week-old rats administered 150 mg/kg of PFOA. While hepatic peroxisomal beta-oxidizing activities were significantly elevated (4-8 fold) in all age groups, catalase activities were only enhanced (30-70%) in 10- and 20-week-old rats compared to control rats. Thus, there appears to be an age-related decline in the induction of catalase by PFOA, while age had no effect on the induction of fatty acid oxidizing enzymes. This could result in elevated hepatic levels of hydrogen peroxide in aged animals compared to young animals as a result of exposure to peroxisome proliferators.

Test substance : PFOA

25.10.2005 (79)

Type : LD50
Value : = 457 mg/kg bw
Species : mouse
Strain : CD-1
Sex : male/female
Number of animals : 120
Vehicle : other: Corn oil
Doses : 250, 500, 750, 1000, 2000, and 4000 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by

intragastric intubation in single doses to 6 groups of male and 6 groups of female young adult mice. Ten male and female mice/group were administered 250, 500, 750, 1000, 2000, or 4000 mg/kg of the test substance. The surviving rats were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Test condition : 10 male and 10 female mice per test group

02.12.2005 (175)

Type : LDLo
Value : = 450 mg/kg bw
Species : dog
Strain : Beagle
Sex : male
Number of animals : 4
Vehicle : no data
Doses : 200 and 450 mg/kg
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Dogs (2/group) received either 200 or 450 mg/kg of the test substance. The following biochemical measurements were made on the blood: sugar, urea nitrogen, total cholesterol, and alkaline phosphatase. When the 450 mg/kg dose was administered, the level of activity of lactic dehydrogenase, isocitric dehydrogenase, aldolase, glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were also measured. A routine hematological examination and an analysis of a 24-hour urine specimen was made at intervals on these animals.

The level of various components of the blood following dosing was compared with an average value observed prior to exposure and with a similar measurement made at the same time on specimens from stock colony dogs. For the enzyme activities, a normal range was established from measurements made on stock dogs. The activity was also measured at least once prior to treatment.

Result : Two male beagles given a single dose of 450 mg/kg APFO died within 48 hours. Plasma enzymes were markedly elevated 24-48 hours after ingestion. Dogs given 200 mg/kg had elevated GPT and GOT in 24 hours which normalized after one week. This increase in plasma enzyme levels is indicative of cellular damage.

Test condition : 2 dogs in each test group

02.12.2005 (160)

Type : LD50
Value : = 178 mg/kg bw
Species : guinea pig
Strain : Dunkin-Hartley
Sex : male
Number of animals : 60
Vehicle : other: Corn oil
Doses : 150, 200, 250, 300, 400, and 670 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to 6 groups of male young adult guinea pigs. Groups of 10 male guinea pigs were administered 150, 200,

250, 300, 400, or 670 mg/kg of the test substance. The surviving guinea pigs were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Test condition : 10 male guinea pigs per test group

16.11.2005 (173)

Type : LD50
Value : = 217 mg/kg bw
Species : guinea pig
Strain : Dunkin-Hartley
Sex : female
Number of animals : 60
Vehicle : other: Corn oil
Doses : 150, 200, 250, 300, 400, and 670 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The test substance, as a suspension in corn oil, was administered by intragastric intubation in single doses to 6 groups of female young adult guinea pigs. Groups of 10 female guinea pigs were administered 150, 200, 250, 300, 400, or 670 mg/kg of the test substance. The surviving guinea pigs were weighed and observed during a 14-day recovery period and then sacrificed. The LD50 values were calculated from the mortality data.

Test condition : 10 female guinea pigs per test group

16.11.2005 (173)

02.12.2005

02.12.2005

02.12.2005

02.12.2005

02.12.2005

5.1.2 ACUTE INHALATION TOXICITY

Type : LC0
Value : > 18.6 mg/l
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 18.6 mg/L
Exposure time : 1 hour(s)
Method : other
Year : 1980
GLP : no data
Test substance : other TS

Method : A group of 5 male and 5 female ChR-CD albino rats weighing 211-264

grams was subjected to a one-hour whole-body inhalation exposure to APFO dust. Material was passed through a 60 mesh sieve and hand packed in a Wright dust feed apparatus. Dry air was passed through the dust feed apparatus. The resulting atmosphere was passed through a 32.3 L glass exposure chamber. The rats were weighed immediately before exposure and on days 1, 2, 4, 7, and 14 days post-exposure. They were then subjected to gross pathologic examination on day 14 post-exposure, serum samples were collected, pooled by sex, and analyzed for both organic and inorganic fluoride content.

Result : No deaths resulted from a one hour exposure to a nominal concentration of FC-143 (18.6 mg/L). Clinical signs during exposure were red nasal discharge, yellow staining of the anogenital fur, dry rales, red material around the eyes, excessive salivation, and lacrimation. Similar signs appeared post-exposure in a 14-day observation period. Bilateral mottling of the lungs was observed in eight of ten autopsies. The pooled serum samples had 42 ppm and 2 ppm of organic fluorine for the males and females, respectively. Inorganic fluoride content was 0.02 ppm for the males and 0.01 ppm for the females.

Test condition : 5 males and 5 females in the test group

Test substance : T-2305 CoC supplied by 3M (Identified by Griffith and Long, 1980 as APFO)

02.12.2005 (94) (285)

Type : LC50
Value : = .98 mg/l
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 36
Vehicle :
Doses : 0.380, 0.810, 0.830, 2.2, 4.8, and 5.7 mg/L
Exposure time : 4 hour(s)
Method : other
Year : 1986
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 6 male Crl:CD rats were exposed head-only to APFO concentrations ranging from 0.380 to 5.7 mg/L for 4 hours. An additional 25 rats were exposed to 0.810 mg/L for use in serial kills. Higher exposure concentrations (2.2 mg/L or more) were achieved by passing 30 liters of air per minute through a high-velocity copper-tubing jet submerged in a mechanically stirred reservoir containing the chemical. Metered carrier and dilution air streams were used to achieve the desired dust concentrations in the 8-liter exposure chamber. For lower exposure concentrations (0.83 mg/L or lower), a falling stream of dust particles from a stirred reservoir impinged on a pneumatic jet. The resultant air stream carried the particles to a cyclone head where larger particles settled back into the reservoir. Dust concentrations were controlled by diluting the main air stream with houseline air before it entered the exposure chamber.

Airborne solids in the chamber were measured by collecting the particulate on membrane filters and determining the weight gain. Concentrations were calculated as time-weighted averages from 5 determinations per 4-hour exposure. Particle size distribution was measured using a Monsanto Cascade Impactor.

Ocular tissues from all exposed rats were studied following fluorescein staining immediately after cessation of exposure. Observations of clinical signs were made daily and body weights were obtained twice weekly. Rats exposed to 0.810 mg/L were killed in groups of 5 on post-exposure days 1, 7, 14, 27, and 42 and were given a gross pathological examination. The

interim kills were used to follow the recovery aspects of lesions produced by acute treatment. Histopathological evaluation was carried out on the lungs, liver, trachea, and gastro-intestinal tract.

Result : Groups of 6 rats were exposed for 4 hours to concentrations of APFO ranging from 0.38 to 5.7 mg/L. At 2.2 mg/L or higher, all rats died within 48 hours after exposure. A single death at 3.8 mg/L was not related to the test material. Two deaths occurred at 0.81 mg/L and one occurred at 0.83 mg/L. APFO exposure produced both an increase in liver size and corneal opacity. Both findings diminished with increasing time after exposure. Liver enlargement reached a maximum 7 to 14 days after exposure returning to normal within 42 days.

Test condition : Head-only exposure
There were 6 rats per test group.

02.12.2005 (163) (373) (374)

02.12.2005

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : = 6959 mg/kg bw
Species : rat
Strain : other: Crl:CD
Sex : male
Number of animals : 15
Vehicle : water
Doses : 3000, 5000, and 7500 mg/kg
Method : other
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Rats were clipped free of hair over the back and trunk area. Five male rats/dose level were dosed with 3000, 5000, and 7500 mg/kg ammonium perfluorooctanoate. The test substance, as a 50/50 aqueous suspension, was applied to the back of each rat under a square of aluminum foil and held in place with elastic bandages. After 24 hours of exposure, the rats were unwrapped, sponged off with a mild detergent, rinsed, dried, and returned to their cages for 13 days observation or until death. During the observation period, the rats were weighed and observed for clinical signs. Gross pathology was done on all survivors and 1 animal that was found dead at 7500 mg/kg. Liver weights were recorded in all rats except 1. The LD50 value was calculated from the mortality data.

Result : Male rats dosed at 3000, 5000 and 7500 mg/kg showed initial weight loss. Rats dosed at 5000 or 7500 mg/kg were lethargic on the day of treatment and the majority had wet and/or stained perineal areas. Chromodacryorrhea was seen in rats dosed at 7500 mg/kg.

Test condition : 5 rats per test group

25.10.2005 (167) (371)

Type : LD50
Value : > 7500 mg/kg bw
Species : rat
Strain : other: ChR-CD
Sex : female
Number of animals : 10
Vehicle : water
Doses : 5000 and 7500 mg/kg
Method : other

Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Rats were clipped free of hair over the back and trunk area. Five female rats/dose level were dosed with 5000 or 7500 mg/kg ammonium perfluorooctanoate. The test substance, as a 50/50 aqueous suspension, was applied to the back of each rat under a square of aluminum foil and held in place with elastic bandages. After 24 hours of exposure, the rats were unwrapped, sponged off with a mild detergent, rinsed, dried, and returned to their cages for 13 days observation or until death. During the observation period, the rats were weighed and observed for clinical signs. Surviving rats were sacrificed.
Result : Female rats dosed at 5000 or 7500 mg/kg showed mild skin irritation and initial weight loss. At 7500 mg/kg a stained face and a wet and stained perineal area were also noted. One of the 5 rats administered 7500 mg/kg died 3 days after treatment.
Test condition : 5 rats per test group
08.11.2005 (170) (371)

Type : LD50
Value : = 4278 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male
Number of animals : 17
Vehicle : water
Doses : 1500, 3000, 5000, and 7500 mg/kg
Method : other
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Rabbits were clipped free of hair over the back and trunk area, and were fitted with plastic collars. Five, 5, 5, and 2 male rabbits were dosed with 1500, 3000, 5000, and 7500 mg/kg ammonium perfluorooctanoate, respectively. The test substance was made into a slurry with water, was applied to the back of each rabbit, and the test site was occluded (wrapped with plastic wrap, gauze, and elastic bandages). After 24 hours of exposure, the animals were unwrapped, washed with water, dried, and returned to their cages for 14 or 15 days observation or until death. During the observation period, the animals were weighed and observed for clinical signs. Gross pathology was done on all survivors and 1 animal that was found dead at 3000 mg/kg. The LD50 value was calculated from the mortality data.
Result : Rabbits were dosed at 1500, 3000, and 7500 mg/kg. Skin irritation occurred at all levels. Clinical signs included weight loss and labored breathing at all levels, wetness underneath the body, cyanosis, diarrhea, and lethargy appearing at most levels.
02.12.2005 (167) (371)

Type : LD50
Value : > 2000 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 2000 mg/kg
Method : other: OECD Guidelines (not otherwise specified)
Year : 1995
GLP : yes

Test substance : other TS

Method : 5 male and 5 female adult albino rabbits of the Hra:(NZW)SPF strain, weighing from 2386 to 2675 grams, were administered a single dermal dose level of 2000 mg/kg of body weight. The test material was applied to the intact skin on each animal's back. The area of application was covered with a gauze patched and secured with paper tape and over wrapped with Saran wrap and Elastoplast tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period. At the end of the exposure period, the collars and bandages were removed and the test sites were washed using tap water and disposable paper towels.

Clinical observations and mortality checks were conducted at approximately 1, 2.5, and 4 hours after test material administration. Additional clinical observations and twice a day mortality checks were conducted daily thereafter for 14 days. Body weight were determined before test material application, at day 7, and at termination of the in-life phase (day 14). The initial dermal irritation reading was made approximately 30 minutes after removal of the test material according to the Draize technique. Subsequent readings of the dermal irritation were made on days 3, 7, 10, and 14. At termination of the in-life phase, all animals were sacrificed and subjected to an gross necropsy examination.

Result : The acute dermal toxicity of T-6342 (assumed to be an aqueous solution of APFO) was tested in male and female rabbits, at a dose level of 2000 mg/kg, and a 24-hour exposure period. All animals appeared normal and exhibited body weight gain throughout the study, with the exception of one male that lost weight during the first week. Dermal irritation consisted of slight to moderate erythema, edema, and atonia; slight desquamation; coriaceousness; and fissuring. No visible lesions were observed upon necropsy. The dermal LD50 in rabbits was determined to be greater than 2000 mg/kg.

Test condition : 5 males and 5 females in the test group
Test substance : T-6342 (purity was not stated)

25.10.2005 (128)

Type : LDLo
Value : = 1000 mg/kg bw
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 12
Vehicle : water
Doses : 100, 1000, and 2000 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 2 male and 2 female adult albino rabbits of the New Zealand breed were administered a single dermal dose level of 100, 1000, or 2000 mg/kg of body weight. The test material was applied to the intact skin on each animal's back. The area of application was wrapped with impervious plastic sheeting to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period. At the end of the exposure period, the collars and test material were removed.

Clinical observations and mortality checks were conducted at approximately 1 and 2 hours after test material administration. Additional clinical observations and mortality checks were conducted daily thereafter for up to 14 days. Body weight were determined before test material application and at termination of the in-life phase (day 14).

Result : In a range-finding study to set doses for a 2-week subchronic dermal study, groups of 4 rabbits were dermally administered 100, 1000, or 2000 mg/kg of FC-143. FC-143 was lethal to 4/4 rabbits at 2000 mg/kg, 3/4 rabbits at 1000 mg/kg, and 0/4 rabbits at 100 mg/kg.

Test condition : 2 male and 2 female rabbits per testing group

25.10.2005 (521)

Type : other: In vitro penetration test
Value :
Species : other: Rat and human epidermal membranes
Strain :
Sex :
Number of animals :
Vehicle : water
Doses :
Method : other
Year : 2005
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Rat and human epidermal membranes were mounted onto in vitro static diffusion cells and skin integrity was confirmed using electrical impedance. APFO was applied to the epidermal surface via the diffusion cell donor chamber and the donor chamber opening occluded with Parafilm. Serial receptor fluid samples were collected with equivalent volume replacement at 0 hours (pre-application), then hourly from 1 to 6 hours, and at 12, 24, 30, and 48 hours and analyzed by liquid chromatography-mass spectrometry for APFO ion.

Result : Rat and human epidermal membranes were mounted onto in vitro static diffusion cells and APFO was applied to the epidermal surface via the diffusion cell donor chamber at a rate of 156 uL/cm2. Serial receptor fluid samples were collected with equivalent volume replacement at 0 hours (pre-application), then hourly from 1 to 6 hours, and at 12, 24, 30, and 48 hours. By 48 hours, only a small portion of the applied material (0.048%) had penetrated the human epidermal membranes. The penetration rate at steady state was 190 ng APFO/cm2/hour. For the rat membranes, the corresponding values were 1.44% and 6499 ng APFO/cm2/hour.

25.10.2005 (260)

28.10.2005

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 189 mg/kg bw
Species : rat
Strain : Fischer 344
Sex : male
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1984
GLP : no data
Test substance : other TS

Method : The acute toxicities of single i.p. injections of PFOA and perfluorodecanoic

(PFDA) acids were evaluated in male Fischer rats. Four groups of rats were used for a more detailed study of toxicity and for analysis of fatty acids from liver, testes and whole blood. One group received a single dose of PFOA; a 2nd, a single dose of 2 mL propylene glycol-water (1:1)/kg (vehicle control); a 3rd, a single dose of NDFDA; the 4th was given 2 mL vehicle/kg and pair-fed with the PFDA group. The first 3 groups were fed ad lib. Rats from each group were killed at 2, 4, 8 and 16 days after dosing for fatty acid analysis.

Result : The LD50/30 day for PFOA was 189 mg/kg and for PFDA was 41 mg/kg. All rats treated with lethal doses of PFOA died within the first 5 days; with PFDA there was delayed lethality, with deaths in the 2nd and 3rd week after dosing. Four groups of rats were used for a more detailed study of toxicity and for analysis of fatty acids from liver, testes and whole blood. One group received a single dose of 100 mg PFOA/kg; a 2nd, a single dose of 2 mL propylene glycol-water (1:1)/kg (vehicle control); a 3rd, a single dose of 50 mg PFDA/kg; the 4th was given 2 mL vehicle/kg and pair-fed with the PFDA group. The first 3 groups were fed ad libitum. Rats from each group were killed at 2, 4, 8 and 16 days after dosing for fatty acid analysis. Rats dosed with PFDA lost half their body weight in 16 days and ate virtually no food from day 7-14 after dosing. Weight loss was less rapid in pair-fed controls. With PFOA there were transient decreases in food intake and body weight which were reversed by day 7. Liver weights of PFOA rats were slightly greater than those from vehicle controls. With PFDA, liver weights were much greater than those from pair-fed controls. In the livers of PFOA rats there were transient increases in oleic and palmitic acids and a decrease in stearic and docosahexenoic acids. These changes were maximum by day 2 and nearly resolved by day 8. With PFDA, similar changes were observed and arachidonic acid and was also greatly decreased. These changes were quantitatively much larger and more persistent.

Test substance : PFOA

02.12.2005 (484) (485) (486) (487)

Type : LD50
Value : = 192 mg/kg bw
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : No information is available regarding the method used.

25.10.2005 (422)

Type : LD50
Value : > 210 mg/kg bw
Species : mouse
Strain :
Sex : female
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other

Year : 1960
GLP : no
Test substance : other TS

Method : In this range-finding procedure, a graded series of doses are administered starting with a unit of 1 and progressing upward or downward as determined by the results, using a factor of 3/2 if the dose is tolerated or 2/3 if the dose proved lethal. The test compound is administered by intraperitoneal injection to female albino mice weighing 20-30 g. Animals are injected with each dose level; mortalities are recorded after 24 hours. From the data, the maximal non-lethal and minimum lethal doses are estimated.
Result : The minimum lethal dose when injected into female mice was 260 mg/kg [3/3 deaths]. The maximum non-lethal dose was 210 mg/kg [0/2 deaths]
Test substance : PFOA
02.12.2005 (559)

Type : other
Value :
Species : rat
Strain : Fischer 344
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : Recent studies in this laboratory and by others suggest that two-dimensional polyacrylamide gel electrophoresis of proteins possesses significant utility in the detection of chemical toxicity and in providing information regarding toxic mechanism. After having identified a set of specific heat-shock and glucose-regulated proteins whose expression in rodent liver and kidney is highly conserved and constitutive, the effect was compared of in vivo (intraperitoneal) exposure to PFOA and PFDA on their expression. The following stress proteins were identified, their x, y coordinate positions mapped, and abundance statistically analyzed and compared: hsp32, hsp60, hsc70, hsp70, hsp90, grp75, grp94, protein disulfide isomerase (PDI), and ER60.
Result : The response to perfluorocarboxylic acids is tissue-, toxicant-, and stress protein class-specific and dose-related. Furthermore, because nearly all of the proteins studied were constitutively expressed at detectable levels in both liver and kidney, the 2-DE stress protein pattern may be suitable to future toxicologic screening applications.
Test substance : PFOA
02.12.2005 (629)

Type : other: Hepatic metabolism
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other

Year : 1993
GLP : no data
Test substance : other TS

Method : P-31 NMR was used to examine the effects of PFDA, PFOA, and clofibrate (CLOF) in both rats and guinea pigs. Male F-344 rats and male Hartley guinea pigs were administered i.p. injections of 150 mg/kg of PFOA, 50 mg/kg (rats) and 100 mg/kg (guinea pigs) of PFDA, or 3 daily doses of 250 mg/kg/day of CLOF. Controls were administered an equal volume of the propylene glycol/water (1:1) vehicle or of saline. Body weight and food consumption were monitored daily, and control animals were pair-fed with dosed partners. All animals were fasted 16-24 hours prior to NMR experiments. P-31 NMR spectra of liver in vivo yield resonances from various phosphorus metabolites including adenosine triphosphate (ATP), phosphomonoesters (PME), and phosphodiesters (PDE).

Result : A marked increase (2-fold) in the PME signal intensity was observed in the PFDA-treated rats, and a slight decrease (25%) is observed in CLOF treatment relative to corresponding controls. In guinea pigs, the mean PME intensity for the PFOA-treated group is one-half of the corresponding control value, while a comparison of PME levels for all other groups are not significantly different. On days 1, 3, and 5 post dose, only the PFDA group shows a deviation from control values, and is significantly different than its control on day 5. ATP levels are not different from control for all treatments at all days. A spectrum of a liver extract from a PFDA-treated rat (day 5 post dose) shows an enhanced signal intensity in the PME region of the spectrum which is a ingle resonance (triplet) at 6.4 ppm. This resonance was identified as phosphocholine (PCho). The increased concentration of liver PCho is a specific response of PFDA-treatment in rats. An increase in this metabolite may be indicative of enhanced phospholipid turnover, specifically phosphatidylcholine. This response does not seem to be related to the presence of peroxisomes since neither PFOA nor CLOF produced an increase in PME. Interestingly, the observed differences between rats versus guinea pigs cannot be accounted for based solely upon species differences in the proliferous capacity for liver peroxisomes.

Test substance : PFOA
02.12.2005 (508)

Type : other: Hepatotoxicity
Value :
Species : rat
Strain :
Sex : male
Number of animals :
Vehicle :
Doses : 150 mg/kg
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : Male rats were dosed with single ip injections of 150 mg/kg PFOA or 50 mg/kg PFDA and liver studies were begun at 1, 3, and 5 days post-treatment with PFOA and 5 days post-treatment with PFDA.

Result : An elevation in liver diacylglycerol (DAG) followed PFDA treatment. These data, along with information from earlier studies, suggested that PFDA induced phosphatidyl-choline (PtdCho) degradation through a phospholipase-C activated mechanism. The results confirmed that PFDA treatment caused a significant increase in the activity of liver phospholipase-C and a decrease in cytidylyltransferase activity both in microsomal and cytosolic fractions. These combined effects are likely

responsible for the accumulation of PtdCho and DAG. These same effects were not observed following exposure to PFOA. The effects were discussed in relation to cellular signaling processes which may provide a mechanism for PFDA induced hepatotoxicity.

Test substance : PFOA

05.12.2005 (513)

Type : other: Inflammation
Value :
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : Recently reported was that systemic administration of PPAR receptor agonists reduced the magnitude of carrageenan-induced edema, in parallel to their reported potencies in vitro. Inflammation following the co-administration of perfluorooctanoic acid (PFOA, a PPAR-alpha agonist) was evaluated with conventional anti-inflammatory agents, dexamethasone or aspirin. Carrageenan was subcutaneously injected into the midplantar hindpaw of male Sprague-Dawley rats, and paw thickness was measured with a micro-caliper to assess edema. PFOA was administered by intraperitoneal injection either before or after the carrageenan administration.

Result : Systemic administration of PPAR receptor agonists reduced the magnitude of carrageenan-induced edema, in parallel to their reported potencies in vitro. Here we evaluated inflammation following the co-administration of perfluorooctanoic acid (PFOA, a PPAR-alpha agonist) with conventional anti-inflammatory agents, dexamethasone (DEX) or aspirin (ASA). We also compared the effects of these agents with L805645, a PPAR-gamma agonist. Carrageenan was subcutaneously injected into the midplantar hindpaw of male Sprague-Dawley rats, and paw thickness was measured with a micro-caliper to assess edema. When intraperitoneally administered 30 minutes prior to carrageenan, paw edema was decreased in a dose-dependent manner with relative potency being PFOA=ASA>DEX. When administered after carrageenan, only PFOA and ASA decreased paw edema with relative potency being PFOA=ASA>>DEX. Interestingly, L805645 reduced edema in a U-shaped dose-response fashion, as lower doses (50-100 mg/kg) decreased edema but a higher (150 mg/kg) dose had no effect -- we speculate that high concentrations of L805645 are associated with the degradation of the PPAR-gamma receptor. In co-administration studies, PFOA enhanced the anti-edema effect of maximally effective doses of DEX, but not ASA. We conclude that PPAR agonists and conventional steroid anti-inflammatory agents regulate inflammation through different mechanisms.

Test substance : PFOA

05.12.2005 (385)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :
Sex : male
Number of animals :

Vehicle	:	
Doses	:	100 mg/kg
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	2002
GLP	:	no data
Test substance	:	other TS
Method	:	The purpose of this investigation was to establish whether proliferation of peroxisomes and mitochondria are necessarily related. Perfluorooctanesulfonate and N-ethyl perfluorooctanesulfonamido ethanol were investigated as peroxisome proliferators in comparison to perfluorooctanoic acid. Three parameters were chosen to assess peroxisome proliferation, stimulation of lauroyl CoA oxidase activity, reduction of serum cholesterol concentration, and hepatomegaly. Mitochondrial biogenesis was assessed through cytochrome oxidase activity, cytochrome content and mitochondrial DNA (mtDNA) copy number. The test materials were administered via a single i.p. injection in male rats, and measurements were made 3 days later.
Result	:	PFOS and PFOA share similar potencies as peroxisome proliferators, whereas N-EtFOSE showed no activity. Mitochondrial biogenesis endpoints were altered only in the PFOA treatment group, which consisted of a decrease cytochrome oxidase activity in liver tissue and an increase in the mitochondrial biogenesis DNA copy number. None of the perfluorooctanoates significantly altered mt cytochrome content following acute in vivo treatment. These data demonstrate that acute administration of PFOS or PFOA causes hepatic peroxisome proliferation in rats. However, stimulation of mitochondrial biogenesis is not a characteristic response of all peroxisome proliferators.
Test substance	:	PFOA

05.12.2005 (89) (90)

Type	:	other: Peroxisome proliferation
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	75 mg/kg
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS
Method	:	The influence of a single 75 mg/kg dose of the peroxisome proliferator, PFOA on hepatic and renal mixed-function oxidase activities has been examined in rats. Peroxisome proliferation is confirmed by increases in peroxisomal palmitoyl-CoA oxidation and carnitine acetyl transferase activity, particularly in liver.
Result	:	Peroxisome proliferation was confirmed by increases in peroxisomal palmitoyl-CoA oxidation and carnitine acetyl transferase activity, particularly in liver. The liver was also more susceptible than the kidney to PFOA-dependent induction of the 12-hydroxylation of lauric acid, suggesting induction of the CYP4A sub-family. This was further confirmed by Western blot analyses, wherein an anti-CYP4A1 antibody revealed a substantial PFOA-dependent induction of CYP4A1 in a pattern similar to that observed for the classical peroxisome proliferator, clofibrate. In addition, using a cDNA probe to CYP4A1 in Northern blot analysis, PFOA

treatment resulted in a marked increase in the steady state level of CYP4A1 mRNA, again more extensively in liver than in kidney. Taken collectively, these data provide evidence that PFOA, like other peroxisome proliferators, is also an inducer of the CYP4A subfamily.

Test substance : PFOA

05.12.2005 (153)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : Increases in acyl coenzyme A (CoA) oxidase activity due to peroxisome proliferation are postulated to cause oxidative stress via elevated production of H2O2, leading to DNA damage. These changes are suspected to be responsible for tumor formation caused by non-genotoxic carcinogens which do not bind to DNA but cause proliferation of peroxisomes. However, the activity of the peroxisomal enzyme acyl CoA oxidase assayed in vitro in the presence of excess fatty acyl CoA substrate may not reflect rates of H2O2 generation in intact liver where fatty acid supply is carefully controlled in part by delivery of substrate. The purpose of this study was to determine if rates of hepatic H2O2 generation were altered in perfused liver and in vivo following induction of H2O2-generating acyl CoA oxidase activity by the intraperitonal injection of the potent peroxisome proliferating agent perfluorooctanoate into rats.

Result : Injection of the potent peroxisome proliferating agent perfluorooctanoate into rats 5 days prior to sacrifice caused an expected 4-fold increase of H2O2-generating acyl CoA oxidase activity measured in hepatic homogenates. In contrast, rates of H2O2 generation in perfused liver measured spectrophotometrically (660-640 nm) through a lobe of the liver were not altered by perfluorooctanoate treatment (7.3 +/- 1.5 vs. 7.8 +/- 0.5 mumol/g/h in livers from untreated control rats). Similar treatment with perfluorooctanoate also increased in vitro acyl CoA oxidase activity 9-fold in livers from deer mice; however, rates of elimination of methanol, a selective substrate for catalase in rodents whose oxidation is limited by the supply of H2O2, were not altered significantly in vivo (control, 110 +/- 11 mumol/g/h vs. perfluorooctanoate, 112 +/- 32 mumol/g/h). Taken together, these data demonstrate that elevation of H2O2 formation by acyl CoA oxidase activity measured in vitro is not necessarily associated with increases in rates of H2O2 generation in intact perfused liver or in vivo, most likely due to rate-limitation in intact cells by fatty acid supply. These data do not support the hypothesis that the induction of peroxisomes leads to excessive H2O2 production and oxidative stress. It follows that alternative hypotheses to explain carcinogenesis caused by peroxisome-proliferating agents need to be considered.

Test substance : PFOA

05.12.2005 (298)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :

Sex : male/female
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 2000
GLP : no data
Test substance : other TS

Method : The potency of the induction of peroxisomal beta-oxidation was compared in perfluorinated fatty acids (PFCAs) with different carbon chain lengths in the liver of male and female rats. Administration to male (intact and castrated) and female rats was by intraperitoneal injection. The activity of peroxisomal beta-oxidation was also determined in cultured hepatocytes prepared from both male and female rats.

Result : In male rats, perfluoroheptanoic acid (PFHA) has little effect, although PFOA, perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) potentially induced the activity. By contrast, PFHA and PFOA did not induce the activity of peroxisomal beta-oxidation in the liver of female rats while PFNA and PFDA effectively induced the activity. The induction of the activity by these PFCAs was in a dose-dependent manner, and there is a highly significant correlation between the induction and hepatic concentrations of PFCAs in the liver regardless of their carbon chain lengths. These results strongly suggest that the difference in their chemical structure is not the cause of the difference in the potency of the induction. Hepatic concentrations of PFOA and PFNA was markedly higher in male compared with female rats. Castration of male rats reduced the concentration of PFNA in the liver while treatment with testosterone entirely restored the reduction. In contrast to the results obtained from the in vivo experiments, the activity of peroxisomal beta-oxidation was induced by PFDA and PFOA to the same extent in cultured hepatocytes prepared from both male and female rats. These results, taken together, indicate that difference in accumulation between PFCAs in the liver was responsible for the different potency of the induction of peroxisomal beta-oxidation between PFCAs with different carbon chain lengths and between sexes.

Test substance : PFOA

05.12.2005 (393)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 2000
GLP : no data
Test substance : other TS

Method : This investigation examined the effects of peroxisome proliferators (PPs) on the biosyntheses of phosphatidylcholine and phosphatidyl-ethanolamine in rat liver. After intraperitoneal exposure to PPs, rats were administered [1-13C]choline + [2-13C]ethanolamine and liver extracts were analyzed by 31P and 13C NMR.

Remark : Cui Z, Houweling M, and Vance DE (1994). Suppression of rat hepatoma cell growth by expression of phosphatidylethanolamine N-

methyltransferase-2. J. Biol. Chem., 269:24531-24533.

Cui Z, Shen YJ, and Vance DE (1997). Inverse correlation between expression of phosphatidylethanolamine N-methyltransferase-2 and growth rate of perinatal rat livers. Biochim. Biophys. Acta, 1346:10-16.

Cui Z, Vance JE, Ming HC, Voelker DR, and Vance DE (1993). Cloning and expression of a novel phosphatidylethanolamine N-methyltransferase: A rat specific biochemical and cytological marker for a unique membrane fraction in rat liver. J. Biol. Chem., 268:16655-16663.

Hatch G and Vance D (1992). Stimulation of sphingomyelin biosynthesis by brefeldin A and sphingomyelin breakdown by okadaic acid treatment of rat hepatocytes. J. Biol. Chem., 267:12443-12451.

Houweling M, Cui Z, Tessitore L, and Vance DE (1997). Induction of hepatocyte proliferation after partial hepatectomy is accompanied by a markedly reduced expression of phosphatidylethanolamine N-methyltransferase-2. Biochim. Biophys. Acta, 1346:1-9.

Houweling M (1991). Phosphatidylcholine metabolism in rat liver after partial hepatectomy. Biochem. J., 278:347-351.

Tessitore L, Cui Z, and Vance DE (1997). Transient inactivation of phosphatidylethanolamine N-methyltransferase-2 and activation of cytidine triphosphate:phosphocholine cytidylyltransferase during non-neoplastic liver growth. Biochem. J., 322:151-154.

Tessitore L, Dianzani I, Cui Z, and Vance DE (1999a). Diminished expression of phosphatidylethanolamine N-methyltransferase 2 during hepatocarcinogenesis. Biochem. J., 337:23-27.

Tessitore L, Sesca E, Bosco M, and Vance DE (1999b). Expression of phosphatidylethanolamine N-methyltransferase in Yoshida ascites hepatoma cells and the livers of host rats. Carcinogenesis, 20:561-567.

Vance DE (1996). Phosphatidylethanolamine N-methyltransferase: Unexpected findings from curiosity-driven research. Eur. J. Med. Res., 1:182-188.

Vance DE, Houweling M, Lee M, and Cui Z (1996). Phosphatidylethanolamine methylation and hepatoma cell growth. Anticancer Res., 16:1413-1416.

Vance DE and Walkey CJ (1998). Roles for the methylation of phosphatidylethanolamine. Curr. Opin. Lipidol., 9:125-130.

Result : Wy-14,643, perfluorooctanoic acid (PFOA), and di(2-ethylhexyl)phthalate (DEHP) are strong, moderate, and weak tumor promoters, respectively, while perfluorodecanoic acid (PFDA) lacks promoter activity. The ratio of choline-derived to ethanolamine-derived phospholipids, Rc/e, was significantly affected by all PPs. Rc/e values were in the order Wy-14,643 > PFOA > DEHP > control > PFDA. The amounts of PtdC derived via the CDP-choline pathway vs. PtdE-N-methyl-transferase (PEMT) activity was 71 vs. 29% in controls. This distribution was significantly affected by treatments with Wy-14,643 (95 vs. 5%), DEHP (87 vs. 13%), and PFDA (39 vs. 61%). Data suggest that Wy-14,643, PFOA, and DEHP cause a preference for choline and the CDP-choline pathway for biosynthesis of PtdC. Additionally, Wy-14,643 and DEHP inhibited the PEMT pathway. In contrast, PFDA-treated rats showed a preference for ethanolamine, and PtdC was predominately synthesized through the PEMT pathway. These data corroborate studies by Vance and co-workers [See Remarks For a Listing of the following references (Cui et al., 1993, 1994, 1997; Hatch and

Vance, 1992; Houweling, 1991; Houweling et al., 1997; Tessitore et al., 1997, 1999a, 1999b; Vance, 1996; Vance et al., 1996; Vance and Walkey, 1998)] which suggest that the pathways for PtdC biosynthesis are important for hepatocarcinogenesis. Further studies to evaluate the potential of these measurements as a biomarker for PP-associated tumorigenesis is warranted.

Test substance : PFOA

05.12.2005 (511)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : This study investigated the effects of the intraperitoneal administration of several peroxisome proliferator-activated receptors (PPARs) subtype-specific agonists on the inflammation and hyperalgesia produced by intraplantar carrageenan injection in unanesthetized male Sprague-Dawley rats. Effects were compared when PPARs were administered 0.5-24 hours before carrageenan, as compared to when it was administered 1.5 hour after carrageenan.

Result : Previous studies have produced conflicting data on the contribution of the peroxisome proliferator-activated receptors (PPARs) to the inflammatory process. This study investigated the effects of several PPAR alpha (PPARa) and PPAR gamma (PPARg) subtype-specific agonists on the inflammation and hyperalgesia produced by intraplantar carrageenan injection in unanesthetized male Sprague-Dawley rats. I.p. administration of PPARa agonists reduced edema in parallel to their potencies determined in vitro. PFOA inhibited carrageenan-induced edema in a dose-dependent manner, and also reduced thermal hypersensitivity. Furthermore, PFOA produced much more robust effects when administered 0.5-24 hours before carrageenan, as compared to when it was administered 1.5 hour after carrageenan. I.p. administration of similar doses of the PPARg agonist Rosiglitazone, but not the less potent agonist, Troglitazone, reduced edema when administered before but not after carrageenan. Thus, systemic administration of potent PPARa and PPARg agonists exert anti-hyperalgesic and/or anti-inflammatory actions in vivo, possibly by interfering with the initiation of inflammation.

Test substance : PFOA

05.12.2005 (592)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other

Year : 1990
GLP : no data
Test substance : other TS

Method : Effects of the peroxisome proliferators PFDA and PFOA on hepatic mitochondrial fatty acid oxidation and CPT activity were examined in vitro and in vivo. PFDA or PFOA was added to isolated rat liver mitochondria in concentrations of 0.2, 2, 20, and 200 ug per mg mitochondrial protein Three days after rats were treated with PFDA or PFOA by intraperitoneal injection (37.5 or 150 umol/kg), liver mitochondria were isolated and examined for hepatic mitochondrial fatty acid oxidation and CPT activity.

Result : PFDA has been hypothesized to cause a diversion of fatty acids from oxidation toward esterification in rat liver. Normal regulation of this partitioning is exerted by carnitine palmitoyltransferase (CTP), an enzyme inhibited by several peroxisome proliferators. PFOA had no effect on CPT activity nor on mitochondrial oxidation of [1-14C]palmitoyl-CoA or [1-14C]palmitoyl-carnitine (quantified by 14CO2 plus acid soluble 14C production. Mitochondrial oxidation of [1-14C]palmitoyl-CoA or [1-14C]palmitoyl-carnitine was unaffected by PFDA or PFOA. CPT activity and inhibition of CPT activity by malonyl-CoA was also unaffected by PFDA or PFOA. Therefore, PFDA and PFOA did not have a major inhibitory effect on hepatic mitochondrial oxidation of palmitoyl-CoA or palmitoyl-carnitine, nor did they interfere with hepatic CPT activity either in vitro or in vivo.

Test substance : PFOA

05.12.2005 (611)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain : Fischer 344
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1994
GLP : no data
Test substance : other TS

Method : A study was conducted on the effects of various peroxisome proliferators on the hepatic immunoglobulin heavy chain binding protein, BiPrp78. BiP/Grp78 was assessed electrophoretically in liver samples from Fisher-344-rats treated by intraperitoneal injection with PFDA, PFOA, clofibrate, or di(2-ethylhexyl)phthalate (DEHP).

Result : Treatment with 50 mg/kg PFDA resulted in the most marked change in the BiP/Grp78 protein. Treatment with this compound resulted in a shift from the basic parent protein species to more acidic forms and this change persisted for up to 30 days after exposure. Treatment with clofibrate resulted in a small decrease in the parent form of the protein. Significant differences were seen between total BiP-Grp78 levels following treatment with 2 mg/kg PFDA and 8 and/or 30 days after treatment with 50 mg/kg PFDA or clofibrate. PFOA and DEHP had less effect in this regard.

Test substance : PFOA

05.12.2005 (630) (631)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain :

Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS

Method : The effect of in vivo exposure to perfluoro-n-octanoic and perfluoro-n-decanoic acids was examined in the rat liver by two-dimensional electrophoresis (2DE). Using non-equilibrium pH-gradient electrophoresis in the first dimension separation, proteins associated with the mitochondrial/peroxisomal cell fraction were observed and immunologically identified.

Result : Conspicuous inductions in peroxisomal enoyl-CoA hydratase and other proteins of the peroxisomal beta-oxidative pathway were observed following single-dose exposure to each compound. The abundance of the tentatively-identified mitochondrial equivalent, crotonase, was not altered by these intoxications. These results confirm previous observations of perfluorocarboxylic acid toxicity and support the use of 2D protein-pattern alterations in biomarker research. The ability to identify this type of alteration via 2DE, in association with specific toxic effects by chemically related compounds, may provide new and additional markers for chemical-induced tissue damage.

Test substance : PFOA

05.12.2005 (627) (632)

Type	:	other: Peroxisome proliferation
Value	:	
Species	:	rat
Strain	:	Fischer 344
Sex	:	male
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	other TS

Method : The toxicity of structurally diverse peroxisome proliferators was investigated using two dimensional protein electrophoresis (2DE). Male Fischer-344-rats were injected intraperitoneally with PFDA, PFOA or clofibrate, or administered di(2-ethylhexyl)phthalate (DEHP) by gavage at levels selected to provide minimal lethality with maximal peroxisome proliferation. After exposure, livers were removed, minced and homogenized. Solubilized protein samples were analyzed using 2DE. Sulfotransferases were identified by immunological techniques.

Result : These compounds differentially change the hepatic expression of proteins identified as aryl- sulfotransferase (ST1A1) and male dominant N-hydroxyarylamine sulfotransferase (ST1C1). Following exposure to peroxisome proliferative doses of PFDA or PFOA, both ST1A1 and ST1C1 abundance in whole liver homogenates was significantly reduced. DEHP and clofibrate had no effect on sulfotransferase expression. The observed down regulation of these sulfotransferases was significant considering their normal detoxication activities. These findings support the unique features of perfluorocarboxylic acid toxicity as it relates to classic peroxisome

proliferators.

Test substance : PFOA

05.12.2005 (628)

Type : other: Peroxisome proliferation
Value :
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1997
GLP : no data
Test substance : other TS

Method : It has been suggested that peroxisome proliferators stimulate Kupffer cells, an effect which may be involved in their mechanism of action. To evaluate this hypothesis, this study was designed to investigate the effect of stimulating Kupffer cells on basal as well as induced peroxisomal enzyme activity. Twenty four hours following treatment of male Sprague-Dawley rats with the peroxisome proliferating agent PFOA, in corn oil or with corn oil alone, hepatic peroxisomal beta-oxidation activity was determined. Stimulating Kupffer cells in vivo by zymosan A (25 mg/kg, i.v.) prior to treatment with corn oil or PFOA was also determined.

Result : Twenty four hours following treatment of male Sprague-Dawley rats with PFOA in corn oil or corn oil alone, hepatic peroxisomal beta-oxidation was 4.6 and 1.8 U/g liver, respectively. PFOA did not influence catalase activity. Stimulating Kupffer cells in vivo by zymosan A (25 mg/kg, i.v.) prior to treatment with corn oil or PFOA diminished basal as well as PFOA-induced peroxisomal beta-oxidation by 20-35%. Activation of Kupffer cells by zymosan A also diminished catalase activity by over 60%. Furthermore, PFOA reduced blood colloidal carbon clearance by 35% within 2 hours of its administration. The data suggest that activation of Kupffer cells exerts a negative effect on basal as well as PFOA-induced peroxisomal enzyme activities. Data also suggest that PFOA inhibits Kupffer cells. Activated Kupffer cells may indeed produce factors which interfere with normal hepatic peroxisomal functions and responses.

Test substance : PFOA

05.12.2005 (651)

Type : other: Peroxisome proliferation
Value :
Species : guinea pig
Strain : Dunkin-Hartley
Sex : male
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1994
GLP : no data
Test substance : other TS

Method : Hepatomegaly was examined in male Wistar rats and male Duncan Hartley guinea pigs treated with one intraperitoneal dose of PFOA or perfluorodecanoic acid.

Result : Male Wistar rats and male Duncan Hartley guinea pigs were treated with one i.p. dose of PFOA or perfluorodecanoic acid (PFDA) resulting in pronounced hepatomegaly in the rat but not the guinea pig. PFDA treatment also resulted in a 4-fold induction of lauric acid 12-hydroxylase activity in the rat but not the guinea pig, indicating induction of the CYP4A subfamily of isoenzymes. Consistent with this latter conclusion, Western blot analysis of rat liver microsomes using an antibody to CYP4A1 and Northern blot analysis of RNA extracts using a CYP4A1 cDNA probe, revealed PFDA-dependent induction of the CYP4A subfamily in the rat but not the guinea pig. Taken collectively, these data have demonstrated that PFDA, like other peroxisome proliferators, is also a CYP4A inducer and conforms to the well-documented species specificity in induction for this class of compound.

Test condition : Male Wistar rats were also included.

Test substance : PFOA

05.12.2005 (119) (273)

Type : other: Peroxisome proliferation

Value :

Species : guinea pig

Strain : Hartley

Sex : male

Number of animals :

Vehicle :

Doses : 150 mg/kg

Route of admin. : i.p.

Exposure time :

Method : other

Year : 1994

GLP : no data

Test substance : other TS

Method : Perfluoro-n-decanoic acid has been shown to enhance phosphomonoester resonance detected by nuclear magnetic resonance spectroscopy in vivo in rats. Whether this effect is shared by other peroxisome proliferators including PFOA and clofibrate was investigated by studying the effects of these three compounds on phosphorus metabolism in male Fischer-344 rats and male Hartley guinea pigs administered a single intraperitoneal dose.

Result : A single dose of 150 mg/kg PFOA in rats and guinea pigs, or 50 mg/kg PFDA in rats and 100 mg/kg PFDA in guinea pigs, or 250 mg/kg CLOF per day for 3 days in both species were not associated with decreased liver viability or significant necrosis. The PME signal was significantly increased only in rats treated with PFDA. This enhanced signal was identified as phosphocholine. Phosphocholine levels in vivo increased steadily from day one to day five post exposure, yielding an intensity on day five which was two times greater than observed in controls. The authors conclude that PFDA is unique among peroxisome proliferators in its effects on liver phospholipid metabolism. Elevated levels of phosphocholine suggest an increase in phosphatidylcholine turnover which may take place through a phosphatidylcholine specific phospholipase-C activated mechanism.

Test condition : Male Fischer 344 rats were also included.

Test substance : PFOA

05.12.2005 (509) (510) (512)

Type : other: Renal clearance

Value :

Species : rat

Strain :

Sex : male/female

Number of animals :

Vehicle :

Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other
Year	:	2002
GLP	:	no data
Test substance	:	other TS
Method	:	Male and female Wistar rats including males and females castrated and ovariectomized, respectively, at 6 weeks of age, had their renal clearance of PFOA determined. Some of the castrated and ovariectomized rats received daily subcutaneous administration of testosterone propionate or beta-estradiol-3-benzoate before intravenous PFOA administration.
Result	:	The biological half-life (t1/2) of perfluorooctanoic acid (PFOA) in male rats is 70 times longer than that in female rats. The difference is mainly due to the difference in renal clearance (CLR), which was significantly reduced by probenecid, suggesting that PFOA is excreted by organic anion transporter(s). Castration of male rats caused a 14-fold increase in the CLR of PFOA, which made it comparable with that of female rats. The elevated PFOA CLR in castrated males was reduced by treating them with testosterone. Treatment of male rats with estradiol increased the CLR of PFOA. In female rats, ovariectomy caused a significant increase in CLR of PFOA, which was reduced by estradiol treatment. Treatments of female rats with testosterone reduced the CLR of PFOA as observed in castrated male rats. To identify the transporter molecules that are responsible for PFOA transport in rat kidney, renal mRNA levels of organic anion transporter 1 (OAT1), OAT2, OAT3, organic anion-transporting polypeptide 1 (oatp1), oatp2, and kidney-specific organic anion transporter (OAT-K) were determined in male and female rats under various hormonal states and compared with the CLR of PFOA. The level of OAT2 mRNA in male rats was only 13% that in female rats. Castration or estradiol treatment increased the level of OAT2 mRNA whereas treatment of castrated male rats with testosterone reduced it. In contrast to OAT2, mRNA levels of both oatp1 and OAT-K were significantly higher in male rats compared with female rats. Castration or estradiol treatment caused a reduction in the levels of mRNA of oatp1 and OAT-K in male rats. Ovariectomy of female rats significantly increased the level of OAT3 mRNA. Multiple regression analysis suggests that the change in the CLR of PFOA is, at least in part, due to altered expression of OAT2 and OAT3.
Test substance	:	PFOA

05.12.2005 (395)

02.12.2005

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 mg
Exposure Exposure	:	
time Number of	:	24 hour(s)
animals	:	6
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Similar to FHSA, Section 1500.41
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Six healthy young adult albino rabbits were used to evaluate the primary skin irritation potential of APFO. The procedure was similar to that described in the Federal Hazardous Substances Act, Section 1500.41. A 0.5 g test sample was applied to 2 intact and 2 abraded sites (dry and moistened), covered with gauze and wrapped with an impervious material. The wrapping was removed after 24 hours and the skin test sites scored according to the Draize procedure immediately and again after 48 hours.

Result : APFO was found to be non-irritating to the skin of albino rabbits when tested per conventional (Draize) procedures. No signs of dermal irritation were noted following a 24-hour contact period of the powder with intact and abraded skin test areas of six animals.

05.12.2005 (95) (285)

Species : rabbit
Concentration : 500 mg
Exposure Exposure :
time Number of : 24 hour(s)
animals : 6
Vehicle : water
PDII :
Result : moderately irritating
Classification : irritating
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Six male rabbits were clipped free of hair on the trunk and lateral areas, and placed in FDA-type stocks. Doses of 0.5 g solid ammonium perfluorooctanoate were applied as an aqueous paste to the intact skin under gauze squares, and the test site was semi-occluded (rubber sheeting was loosely wrapped around the trunk and secured with adhesive tape). After 24 hours, the rabbits were removed from the stocks, the patches removed, and the reactions observed. Observations were also made at 48 hours.

Result : After 24 hours of semi-occluded contact, APFO caused mild to moderate skin irritation. Observation at 48 hours indicated slight to moderate irritation.

05.12.2005 (166) (371)

Species : rabbit
Concentration : 500 mg
Exposure Exposure : Occlusive
time Number of : 3 minute(s)
animals : 9
Vehicle :
PDII :
Result : highly irritating
Classification : corrosive (causes burns)
Method : other: Modeled after that of Draize et al., 1965
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Young adult albino rabbits of the New Zealand breed were used to evaluate the primary skin irritation potential of APFO. A 0.5 g test sample was applied to 2 intact and 2 abraded sites (dry and moistened), covered with gauze and wrapped with an impervious material. The wrapping was removed after 3 minutes, 1 hour, or 4 hours. One, 24, and 48 hours after removal of the test material the test sites were examined for irreversible damage and scored separately for erythema and edema on a graded scale

of 0-4.

Result : APFO produced irreversible tissue damage in female rabbits, following a 3-minute, 1-hour, and 4-hour contact period. Moderate erythema and edema, as well as chemical burn, eschar, and necrosis, were observed following all three contact periods.

Test condition : 3 rabbits per test group

05.12.2005 (523)

Species : rabbit
Concentration :
Exposure Exposure : Occlusive
time Number of : 24 hour(s)
animals : 21
Vehicle :
PDII :
Result : not irritating
Classification : not irritating
Method : other
Year :
GLP : no
Test substance : other TS

Method : Twenty-one male rabbits were clipped free of hair over the back and trunk areas, and fitted with plastic collars. Ammonium perfluorooctanoate impregnated Teflon® strips or ammonium perfluorooctanoate impregnated Kevlar® strips were applied to the back of each rabbit. Three rabbits served as controls and were wrapped in non-ammonium perfluoro-octanoate-treated material. The trunk of each rabbit was then occluded (wrapped with a layer of plastic wrap, gauze stretch bandage, and adhesive stretch tape). After 4-, 8-, or 24-hour exposure periods, the wrappings were removed and the exposed areas were wiped with gauze pads that were soaked in a 50:50 ethanol:water solution. The animals were observed after unwrapping for skin irritation.

Result : No skin irritation was observed.

Test condition : Test groups were comprised of 9 male New Zealand white rabbits; the Control group contained 3 New Zealand white rabbits.

Test substance : C-8 impregnated Teflon or Kevlar strips.

05.12.2005 (190)

Species : rat
Concentration :
Exposure Exposure :
time Number of :
animals :
Vehicle :
PDII :
Result :
Classification :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : To elucidate the site of action of PFOA in the carrageenan model of peripheral inflammation, male Sprague-Dawley rats were administered PFOA, acetylsalicylic acid, or dexamethasone after the intraplantar injection of carrageenan (1%). The anti-edema effects of systemic PFOA (50-150 mg/kg, i.p.) were compared with prototypical nonsteroidal (acetylsalicylic acid, ASA, 50-200 mg/kg) and steroidal (dexamethasone, 0.5-5.0 mg/kg) drugs after the intraplantar injection of carrageenan (1%). The anti-edema effects of systemic PFOA were compared with local intraplantar (10 mg/kg), and intracerebroventricular (0.1-50 ug) routes of

administration.

Result : Systemic PFOA was at least as or more efficacious than ASA or dexamethasone in reducing carrageenan-induced edema. RU-486 did not change the anti-edema effect of PFOA, ruling out a contribution of endogenous release of glucorticoids. Intracerebroventricular PFOA dramatically reduced multiple signs of inflammation at doses well below the systemically-effective dose. The anti-edema effect of high systemic doses of PFOA (100 mg/kg or more, i. p.) is mediated in part by actions in the brain.

Test substance : PFOA

05.12.2005 (593)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment : not rinsed
Number of animals : 2
Vehicle : none
Result : moderately irritating
Classification : irritating
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : One-tenth mL (38.3 mg) of solid test substance was placed into the right conjunctival sac of each of 2 rabbits (sex not specified). After 20 seconds, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, and at 1, 2, 3, 7, 14, 21, and 28 days. Fluor-I-strip® stain and a biomicroscope were used at examinations after the day of treatment.

Result : APFO caused generalized moderate corneal opacity with a small area of severe opacity, intermittent moderate iritis and moderate conjunctivitis when 38.3 mg of solid test material was placed into the right conjunctival sac of a rabbit's eye. The ocular effects gradually receded, however, the small area of corneal opacity persisted and at 21-28 days was mild with vascularization. An eye dosed with the test material and promptly washed had a small area of slight to moderate corneal opacity and moderate to slight conjunctivitis with no iritic effect. The eye was normal within seven days except for mild conjunctival redness, which was normal within 14 days.

Test condition : 1 rabbit in unrinsed group and 1 in washed group

08.11.2005 (165)

Species : rabbit
Concentration : undiluted
Dose : .1 other: gram
Exposure time : .5 minute(s)
Comment : rinsed after (see exposure time)
Number of animals : 6
Vehicle :
Result : moderately irritating
Classification : irritating
Method : other: FHSA, Section 1500.42
Year : 1976
GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Method : Six healthy young adult albino rabbits were used to evaluate the eye irritation potential of APFO according to the FHSA, Section 1500.42. A 0.1 g sample was instilled in the conjunctival sac of the right eye of each test animal. The left eyes remained untreated and served as control. The eyes were examined and scored at 1, 24, 48, and 72 hours and 5 and 7 days post-instillation.

In a subsequent study, another six healthy young adult albino rabbits were used to evaluate the effect of washing the treated eyes with water after limited contact with APFO. After instillation of 0.1 g of sample, the eyes of 3 rabbits were washed with 200 mL of water after 5 seconds of contact and the remaining 3 were similarly washed after 30 seconds. Again, untreated eyes served as controls. The eyes were examined and scored as above.

Remark : The test material was rinsed from the eyes in 3 rabbits after 5 seconds with 200 cc of water and after 30 seconds in 3 rabbits with 200 cc of water. The treated eyes were examined at 1, 24, 48, and 72 hours and 5 and 7 days following instillation of the test material into the eyes.

Result : APFO (100 mg) was moderately irritating to the eyes of rabbits (mean score = 14.0; highest possible score = 110.0). Iridial and conjunctival effects were evident in unwashed eyes, but only conjunctival effects appeared when eyes were washed after exposure. By day 7, 4/6 eyes were free of irritation. The mean irritation score at that time was 2.0/110

16.11.2005 (97) (285)

Species : rabbit
Concentration : 100 mg
Dose :
Exposure time :
Comment :
Number of animals : 6
Vehicle : none
Result : irritating
Classification : irritating
Method : other: FHSA, Section 1500.42
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Six healthy young adult albino rabbits were used to evaluate the eye irritation potential of APFO according to the FHSA, Section 1500.42. A 0.1 g sample was instilled in the conjunctival sac of the right eye of each test animal. The left eyes remained untreated and served as control. The eyes were examined and scored at 1, 24, 48, and 72 hours and 5 and 7 days post-instillation.

Result : All 6 treated rabbits exhibited moderate corneal opacity, iritis, and conjunctivitis. No change in the ocular effects was seen after 7 days.

28.10.2005 (99)

Species : rabbit
Concentration : 100 mg
Dose :
Exposure time :
Comment :
Number of animals : 6
Vehicle : none
Result : irritating
Classification : irritating
Method : other: FHSA Section 1500.42
Year : 1976
GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Method : Six healthy young adult albino rabbits were used to evaluate the eye irritation potential of APFO according to the FHSA, Section 1500.42. A 0.1 g sample was instilled in the conjunctival sac of the right eye of each test animal. The left eyes remained untreated and served as control. The eyes were examined and scored at 1, 24, 48, and 72 hours and 5 and 7 days post-instillation.

Result : All 6 rabbits exhibited iritis and conjunctivitis. No corneal effect was seen. The iritic effects cleared in 4 of the 6 rabbits by 5 days after treatment; the iritis in the other 2 rabbits remained unchanged. The conjunctivitis also cleared in 4 of the 6 rabbits by day 5 and in 1 of the other 2 rabbits by day 7; the conjunctivitis in the remaining rabbit was slowly receding.

28.10.2005 (98)

5.3 SENSITIZATION

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction .4 other: mL occlusive epicutaneous
2nd: Challenge .4 other: mL occlusive epicutaneous
3rd:
Number of animals : 102
Vehicle : water
Result : not sensitizing
Classification : not sensitizing
Method : EPA OPPTS 870.2600
Year : 2001
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : APFO was tested for its dermal sensitization potential by the Buehler method in guinea pigs. The moistened test material was topically applied for 6 hours to 20 healthy guinea pigs, once each week for a 3-week induction period. A test vehicle control group of ten guinea pigs was maintained under the same environmental conditions and treated with the vehicle (distilled water) for the induction phase. 27 days after the first induction dose, a challenge dose of the test substance (50% in water) and vehicle were applied to a naive site on each of the test and test substance irritation control guinea pigs. Approximately 24 and 48 hours after each induction and challenge dose, the test and test irritation control animals were scored for erythema.

Result : In the induction phase, very faint to faint erythema was noted. In the challenge phase, very faint erythema was observed as in the induction phase. Based on these findings, APFO was not considered to be a skin sensitizer.

Test condition : Induction phase application was once each week for 3 weeks of 0.4 mL of a 90% mixture of the test substance in distilled water, occluded, for 6 hours.

Test groups were comprised of 20 male guinea pigs, control groups were comprised of 10 male guinea pigs, and preliminary irritation groups contained 4 male guinea pigs.

Challenge phase was 27 days after the first induction dose.

The procedures used were validated using alpha-hexylcinnamaldehyde as a positive control substance. The positive control group was comprised of 10 male guinea pigs with another group of 5 male guinea pigs in the positive vehicle control group.

05.12.2005 (213)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: ChR-CD
Route of admin.	:	inhalation
Exposure period	:	2 weeks
Frequency of treatm. Post	:	6 hours a day, 5 days a week
exposure period	:	42 days
Doses	:	11 or 83 mg/m3
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1979
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Houseline air (approximately 20 L/min) was passed through a cyclone-head dust generator connected to a particle agitator-reservoir that contained ammonium perfluorooctanoate. The resulting airborne particulate was passed into a 30 L battery jar exposure chamber. The atmospheric concentration of ammonium perfluorooctanoate in the exposure chamber was monitored at 30-minute intervals. Rats were exposed, head only, for 5 consecutive days, 6 hours per day. After 5 days, the rats were given a 2-day recovery (weekend), which was followed by 5 daily, consecutive 6-hour exposures. All rats were weighed and observed daily (except weekends) during the exposure and recovery periods. Food and water were available ad libitum at all times other than during the actual exposure.

Clinical laboratory examinations were performed on 10 rats from each group at 0, 14, and 28 days post-exposure. After a total of 10 exposures, tissues from 5 rats from each group were evaluated for potential pathologic changes at 0, 14, 32, and 42 days post-exposure. Organs were weighed, and absolute and relative organ weights were calculated. On the 5th and 9th days of exposure, 10 rats were selected from each group for eye examinations.

Result : Groups of 20 rats were exposed, head only, to particular atmospheres of 11 or 83 mg/m3 of C-8, six hours a day, five days a week for two weeks. The exposed rats showed a dose-related suppression of body weight. Liver injury or dysfunction was suggested by dose-related elevations of plasma enzymes for up to 28 days after the last exposure. Liver degeneration was detected histologically at the end of the exposure period. These liver effects were not observed after 14, 32 or 42 days of recovery. Eye examinations revealed no compound-related effects.

Test condition : Test and control rats were exposed head-only. Controls were exposed only to air.

There were 20 male rats in the control and test groups.

5 rats from each of the 3 groups were pathologically evaluated at 0, 14, 32, and 42 days post-exposure.

05.12.2005 (164) (373)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: Crl:CD
Route of admin.	:	inhalation

Exposure period	:	2 weeks
Frequency of treatm. Post	:	6 hours a day, 5 days a week
exposure period	:	84 days
Doses	:	1, 7.6, and 83.9 mg/m3
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1981
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Dust atmospheres of ammonium perfluorooctanoate were generated by passing air through a glass generator. For the high concentration (84 mg/m3), chamber atmosphere concentrations were primarily determined by gravimetric analysis. For the intermediate and low concentrations (8 and 1 mg/m3, respectively), chamber atmospheres were determined by a chemical analyses. Male rats (age 7-8 weeks, weighing 240-279 g) were exposed head-only to dust atmospheres for 6 hours/day, 5 days/week for 2 weeks (weekends excluded). During exposure, rats were observed and clinical signs were noted. Post-exposure rats were weighed and observed daily for 14 recovery days, then weighed and observed 2 times/week through 84 days of recovery. Five rats/group were sacrificed at 0, 14, 28, 42, and 84 days of recovery, for a total of 96 test days.

Clinical laboratory examinations were performed on 5 rats from each group at 0, 14, 28, 42, and 84 days post-exposure. After a total of 10 exposures, tissues from 5 rats from each group were evaluated for potential pathologic changes at 0, 14, 28, 42, and 84 days post-exposure.

The rats were examined grossly and tissues and organs were saved for microscopic evaluation. In addition, lungs, heart, thymus, spleen, liver, testes, and kidneys were weighed. At necropsy, blood was collected for analysis of organofluoride levels in rat blood. Blood samples from the 0 and 84 mg/m3 groups were analyzed at each recovery period. Blood samples from the 1 and 8 mg/m3 groups were analyzed only at 0 and 28 recovery days.

Result : Groups of rats were exposed six hours a day, five days a week for two weeks to 1.0, 7.6 or 83.9 mg/m3 of C-8. Observations of clinical signs during exposure showed only slight nasal and ocular discharge. However, after three to four days on test at 83.9 mg/m3 one rat died during exposure and another was sacrificed in extremis. Both of these rats had lost a considerable amount of weight. Body weight of the 1.0 mg/m3 groups were similar to those of the controls while the body weights of the 7.6 mg/m3 group were significantly higher. Organ to body weight ratios demonstrated a dose-related significant increase in lung, liver and testes weight immediately after exposure ended. The liver/body weight ratios were significantly higher in the 83.9 mg/m3 group through a 28-day recovery period. Clinical laboratory measurements demonstrated an increase in serum alkaline phosphatase in all exposure groups after ten exposures, which persisted in the 83.9 mg/m3 group through 14 days of recovery. Pathological evaluation revealed heavy livers and microscopic lesions in the 7.6 and 83.9 mg/m3 groups. These changes were reversible following a 28-day recovery period. Blood fluoride analysis clearly demonstrated a dose-related presence of C-8 in all groups including the controls. The amount of C-8 in blood decreased with time, but was detectable after 84 days recovery in both controls and the 83.9 mg/m3 group (the initial blood level of C-8 in the 83.9 mg/m3 group was 108 ppm falling to 0.84 ppm after 84 days with a half-life of 5-7 days; in the 1 mg/m3 group an organo fluoride level of 13 ppm was detected immediately after the last exposure.

Test condition : There were 24 male rats in the test and control groups.

The exposures were head-only.

Control rats were exposed only to air.

Post-exposure, rats were weighed and observed daily for 14 days of recovery, then weighed and observed twice a week through 84 days of recovery. By design, 5 rats per group were sacrificed at 0, 14, 28, 42, and 84 days recovery, for a total of 96 test days.

05.12.2005 (172) (373) (374)

Type : Sub-chronic
Species : rat
Sex : male
Strain : other: Crl:CD BR
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period : 56 days
Doses : 30 and 300 ppm
Control group : yes, concurrent no treatment
Method : other
Year : 1995
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Rats were approximately 6 weeks old at arrival. At study start, the body weights ranged from 196 to 240 g. Rats were housed singly and were fed food and water ad libitum. During the test period each group were fed diet that contained 0, 30, or 300 ppm of the test substance. Diets were prepared once for the 2-week feeding period and were stored refrigerated until used. All rats were weighed and observed for clinical signs of toxicity. Rats not sacrificed at the end of the feeding period were weighed and observed during the recovery period. Cage-side examinations to detect moribund or dead rats were conducted twice daily. Five rats/group were sacrificed at the end of the 14-day feeding period, and on recovery days 7, 28, and 56. Livers were removed and weighed at each sacrifice period. Blood samples were taken for organofluoride concentration analysis from rats sacrificed at the end of the feeding period and on recovery day 7. Appropriate statistical methods were used to analyze body weights, body weight gains, and organ weight data.

Result : Groups of 20 male rats were fed diets containing 30 or 300 ppm of APFO for 14 days. Rats were sacrificed at the end of the feeding period and on recovery days 7, 28, and 56. No deaths occurred during this study. Clinical signs of toxicity, seen in both the 30 and 300 ppm groups, included irregular respiration, rapid breathing, red nasal discharge, and hunched posture. Significant decreases in mean body weights were observed in rats administered 300 ppm of APFO. Significant increases in mean absolute liver weights were observed in both groups when sacrificed at the end of the 14-day study and on recovery day 7, and in the 300 ppm dose group rats sacrificed on day 28. Mean blood fluoride concentrations of rats sacrificed on recovery day 0 were 0.30 ppm in control rats, 33.23 ppm in the 30 ppm group, and 71.52 ppm in the 300 ppm group. On recovery day 7, mean blood fluoride concentrations were 0.94 ppm for controls, 19.26 ppm for the 30 ppm group, and 22.20 ppm for the 300 ppm group.

Test condition : Test groups were comprised of 20 male rats.

05.12.2005 (200)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : other: Charles River CD Albino
Route of admin. : oral feed
Exposure period : 28 days

Frequency of treatm.	:	Daily
Post exposure period	:	None
Doses	:	30, 100, 300, 1000, 3000, 10,000, or 30,000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : In a 28-day study of ChR-CD albino rats, eight randomly assigned groups of five males and five females were studied. After rats were allowed to acclimate for a week in individual cages they then received similar feed containing 0, 30, 100, 300, 1000, 3000, 10,000, or 30,000 ppm APFO for 28 days. The animals were observed daily and body weights and food consumption were recorded weekly.

Animals that died during the study were examined for gross pathology, as were surviving animals at 28 days. It is stated that the study included a complete examination of gross pathology and a complete set of tissues and organs were examined, but the specific list is not supplied. Livers were weighed to determine relative organ weight then stained for histopathologic examination.

Result : All animals in the 10,000 and 30,000-ppm groups died before the end of the first week. There were no premature deaths or other clinical signs of toxicity in the other groups. Body weight gains were reduced in the groups receiving 1000 ppm or more. Slight reductions in body weight gain were also observed in males exposed to 300 ppm and males and females fed 100 ppm. Reduced food intake was observed in rats fed 1000 ppm or higher in a dose-related manner. Relative liver weights were increased in males fed 30 ppm or more and females fed 300 ppm or more.

Gross pathological exam did not reveal treatment-related effects in kidneys or other organs besides livers. Focal to multifocal cytoplasmic enlargement of hepatocytes was noted in animals fed 300 ppm, and multifocal to diffuse enlargement of hepatocytes was noted in animals fed 1000 ppm or higher. These effects were more pronounced in males.

Test condition : Test and control groups were comprised of 5 male and 5 female rats each.

05.12.2005 (331)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other: Charles River CD rats
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	10, 30, 100, 300, or 1000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 100 ppm
LOAEL	:	= 300 ppm
Method	:	other
Year	:	1978
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : In a 90-day feeding study, 60 ChR-CD albino rats, 30 of each sex, were randomly divided into 6 groups of 5 males and 5 females. The animals were placed in individual cages for a pretest conditioning period during which Purina Laboratory Chow and water were available ad libitum. They then received similar feed containing 0, 10, 30, 100, 300, or 1000 ppm APFO. Observations for signs of toxicity were made daily; body weights

and food consumption were recorded each week.

Once during pretest and at one and 3 months, orbital sinus blood and urine were collected following overnight fasting. Hematology included hemoglobin, hematocrit, total erythrocytes, reticulocytes, and total and differential leucocyte count. Biochemical evaluations were for fasting blood glucose, blood urea nitrogen, plasma glutamic pyruvic transaminase, plasma glutamic oxalacetic transaminase, plasma alkaline phosphatase, gamma-glutamyl peptidase, creatinine phosphokinase, and calcium. Urinalysis included color and appearance, volume, pH, specific gravity, qualitative tests for protein, glucose, ketone, bilirubin, occult blood, and microscopic examination. Serum samples were collected before sacrifice and pooled by group and sex for APFO analysis.

The animals were sacrificed by carbon dioxide inhalation and subjected to gross pathologic examination. Absolute and relative organ weights were determined for spleen, liver, kidney, adrenals, and pituitary. The thyroid/-parathyroid was weighed after fixation. Tissues were preserved in 10% neutral buffered formalin (eyes in Russel's fixative). One liver sample of each sex from the 300 ppm group was analyzed for organic fluorine content.

Histologic examinations of the following tissues were performed in all rats in the control, 100, 300, and 1000 ppm groups: lumbar spinal cord, salivary gland, brain and cervical cord, small intestines (duodenum, jejunum, ileum), peripheral nerve, eyes, colon, pituitary, pancreas, thyroid with parathyroid, liver, adrenals, kidneys, lung, urinary bladder, heart with coronary vessels, testes, aorta, ovaries, spleen, prostate, mesenteric lymph node, uterus, thymus, skin (mammary gland, bone with marrow (sternum), and any tissue(s) with gross lesions.

The livers from rats from the 10 and 30 ppm dosage level were also microscopically examined.

Statistical analysis compared the treatment groups with the control group by sex. The results were compared by analysis of variance (one-way classification) using Bartlett's test for homogeneity and the appropriate t-test for equal or unequal variances using multiple tables to judge significance of differences.

Result : No changes considered to be directly related to APFO were seen in general behavior, appearance or survival. A slight decrease in body weight gain and food consumption was seen for male rats in the 300 and 1000 ppm groups. Hematologic, biochemical and urinalysis values for the female rats showed no changes considered to be related to APFO. A few values obtained for the males showed a slight deviation from the control values (i.e. slightly lower erythrocyte count, and elevated blood urea nitrogen and alkaline phosphatase values). Compound-related gross observations such as enlargement and varying degrees of discoloration on the surface of the liver were observed among male rats in the 1000 ppm group. There were no such observations among female rats from the 1000 ppm group or in males or females from lower dietary levels. Statistically significant variations in sex-group mean organ weights, which were considered compound-related, occurred in liver of rats in the 300 and 1000 ppm groups. All other variations were unaccompanied by any morphologic alterations. Microscopically, compound-related lesions were confined to the liver. The lesions consisted of focal to multifocal, very slight to slight, cytoplasmic enlargement of hepatocytes located in centrilobular-midzonal regions of the affected liver lobules, accompanied in some instances by increased amount of yellowish-brown pigments resembling lipofuscin in cytoplasm of hepatocytes and occasionally in sinusoidal lining cells. The incidence and relative severity of the above lesions were predominantly among males and more pronounced among rats at 1000 ppm. The other

changes recorded in the liver and other tissues were lesions of naturally occurring diseases and they were present in most instances among the control and test rats.

Test condition : Test and control groups were comprised of 5 male and 5 female rats each.

05.12.2005 (285) (338)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: Crl:CD BR
Route of admin.	:	oral feed
Exposure period	:	13 weeks
Frequency of treatm. Post	:	Daily
exposure period	:	8 weeks
Doses	:	1, 10, 30, and 100 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 1 ppm
Method	:	other
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The purposes of this study was to assess the sub-chronic toxicity of APFO when fed to rats for at least 13 weeks and to evaluate reversibility of any toxic effects after approximately 8 weeks without treatment. There were 320 male Crl:CD BR rats assigned at random to 6 groups (55/group in Groups 1 through 5, 45/group in Group 6) and fed diets containing 0 (non-pair-fed control), 1, 10, 30, 100, or 0 ppm (control group pair-fed to the group fed 100 ppm) for up to 13 weeks. In addition, 10 animals/sex/group in Groups 1 through 5 (designated as recovery animals) were fed basal diet for 8 weeks post-treatment.

The animals were observed at least twice daily. Body weights were recorded once before initiation of treatment, weekly thereafter, and on the day of necropsy. Food consumption was recorded weekly for animals given 1, 10, or 30 ppm and for the pair-fed groups (animals given 0 or 100 ppm). Food consumption was recorded weekly for all groups during recovery.

There were 15 animals/group sacrificed after 4, 7, or 13 weeks of treatment; 10 animals/group in Groups 1 through 5 were sacrificed after 13 weeks of treatment and 8 weeks without treatment. Hepatic CoA Oxidase activity was determined for 5 animals/group at each scheduled sacrifice.

Serum samples from 10 animals/group were collected at each scheduled sacrifice during treatment and from 5 animals/group during recovery for hormone analysis. Non-fasted rats were anesthetized with methoxyflurane and blood was collected from the descending vena cava. These samples were analyzed for estradiol, testosterone (total) and luteinizing hormones, and for test material content.

One animal given 100 ppm was sacrificed during Week 4 due to severe neck sores; all other animals survived to scheduled sacrifice.

Result : Body weight and cumulative body weight gain for the 100 ppm rats were significantly lower than those of the control group. Hepatic palmitoyl CoA oxidase activity was significantly increased in rats administered 30 and 100 ppm of APFO, and rats administered 10 ppm had transiently higher levels. Enzyme levels after 8 weeks of recovery following the 13 weeks of dietary administration were not significantly different from those of the controls. Administration of APFO caused increased absolute and relative liver weights and hepatocellular hypertrophy in the livers of rats administered 10, 30, or 100 ppm of APFO after 4, 7, and 13 weeks of treatment. The

progression of hepatocellular hypertrophy did not appear to be affected by the length of treatment. The changes observed are suggestive of a compound-related effect on intracellular metabolism and may be associated with peroxisome proliferation. At the end of recovery, these changes were not observed, indicating that the increase in liver weights was reversible. There was no consistent pattern for the hormone determinations which could be attributed to APFO administration. None of the hormone levels were significantly different from controls although there appeared to be some indication of elevated estradiol for the 100 ppm group at the week 5 determination. The NOAEL was 1 ppm.

Test condition : Both a nonpair-fed control group and a pair-fed control group were included in this study.

There were 55 male rats in the test and nonpair-fed control groups and there were 45 male rats in the pair-fed control group.

05.12.2005 (314) (496) (497)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Wistar
Route of admin. : oral feed
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : The influence of the peroxisomal proliferators PFOA, perfluorooctane sulfonic acid (PFOSA) and clofibric acid on lipid metabolism in rats was studied.

Result : Dietary treatment of male Wistar rats with these three compounds resulted in rapid and pronounced reduction in both cholesterol and triacylglycerols in serum. The concentration of liver triacylglycerols was increased by about 300% by PFOSA. Free cholesterol was increased by both perfluoro compounds. Cholesteryl ester was reduced to 50% by PFOSA as well by clofibrate. In hepatocytes from fed rats, all the compounds resulted in reduced cholesterol synthesis from acetate, pyruvate and hydroxymethyl glutarate, but there was no reduction of synthesis from mevalonic acid. The oxidation of palmitate was also increased in all groups. The perfluoro compounds, but not clofibrate, caused some reduction in fatty acid synthesis. The activity of liver HMG-CoA reductase was reduced to 50% or less in all treatment groups and all three compounds led to lower activity of acyl-CoA:cholesterol acyltransferase (ACAT). Changes in other enzymes related to lipid metabolism were inconsistent. The present data suggest that the hypolipemic effect of these compounds may, at least partly, be mediated via a common mechanism; impaired production of lipoprotein particles due to reduced synthesis and esterification of cholesterol together with enhanced oxidation of fatty acids in the liver.

Test substance : PFOA

05.12.2005 (312)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : oral feed
Exposure period : 2 weeks

Frequency of treatm.	:	Daily
Post exposure period	:	
Doses	:	0.02%
Control group	:	
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	other TS

Method : The induction of peroxisome proliferation in rat liver was examined after administration of PFDA, PFOA, perfluoro-n-butyric acid (PFBA, C4), 1-H,1-H-pentadecafluoro-n-octanol (PFOL, C8) perfluorododecane (PFD, C12), and perfluorooctane (PFO, C8). The peroxisome proliferation in the liver was detected by the following methods; 1) measurement of liver weight, 2) assay of hepatic catalase activity, 3) analysis of 600 X g supernatant of liver homogenates by SDS-polyacrylamide gel electrophoresis to observe the induction of the bifunctional enoyl-CoA hydratase in peroxisomes (80K-protein) and 4) observation by electron microscopy.

Result : The oral administration of diets containing 0.02%-PFOA and PFBA to male rats of the Sprague-Dawley strain for 2 weeks and the single intraperitoneal injection of corn oil mixed with PFDA, PFOA, and PFOL at the dose of 100 mg/kg induced peroxisome proliferation markedly. PFOL, which has two hydrogen atoms around the hydroxylated carbon, should be metabolized to PFOA, which is an active inducer. Perfluorinated paraffins, PFD and PFO, did not show any induction, indicating the importance of the carboxylic group in the molecule for the peroxisome proliferation. Although the participation of thyroid hormone cannot be excluded, PFOA appears to act directly on the liver.

Test substance : PFOA

05.12.2005 (330)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	
Control group	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS

Method : Male and female rats were fed a diet containing 0.01% (w/w) perfluorooctanoic acid (PFOA) for 2 or 26 weeks, and the effects on enzymes that participate in the metabolism of peroxides and xenobiotics in liver were studied.

Result : Elevated activity of peroxisomal beta-oxidation persisted throughout the treatment of male rats with PFOA for 26 weeks. The activity of glutathione (GSH) peroxidase towards hydrogen peroxide was depressed significantly by the prolonged administration. The long-term treatment of male rats with PFOA decreased the activity of GSH peroxidase towards cumene hydroperoxide and increased the activity of microsomal NADPH-dependent lipid peroxidation. The activities of GSH reductase and hepatic content of GSH remained unchanged. There was no difference in the content of conjugated dienes in microsomal lipid between male rats exposed to PFOA for 26 weeks and age-matched control. The activities of GSH S-transferase towards 1-chloro-2,4-dinitrobenzene and 1,2-dichloro-4-nitrobenzene were depressed by the short-term administration of PFOA to male rats, and this

inhibition became pronounced during the prolonged treatment. Microsomal cytochrome P450 was induced by the short-term treatment of male rats with PFOA, and elevated levels persisted throughout the treatment for 26 weeks. Upon the administration of PFOA to male rats for 2 weeks, the activity of 7-ethoxycoumarin O-deethylase was increased markedly, whereas the activities of either aniline p-hydroxylase or aminopyrine N-demethylase were unchanged. Although an age-dependent decrease was observed in the activity of 7-ethoxycoumarin O-deethylase, the activity in male rats treated with PFOA for 26 weeks was higher than that of age-matched control, to the same extent as was observed with the short-term treatment. The prolonged administration of PFOA to male rats caused a significant increase in the activity of both aniline p-hydroxylase and aminopyrine N-demethylase. Little change was found in the same parameters tested in female rats even after the prolonged administration of PFOA.

Test substance : PFOA

05.12.2005 (362)

Type : Sub-chronic
Species : rat
Sex : male
Strain :
Route of admin. : oral feed
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1995
GLP : no data
Test substance : other TS

Method : Male rats were fed a diet that contained PFOA and PFDA at concentrations ranging from 0.0025-0.04% (w/w) and from 0.00125-0.01% (w/w), respectively, for 1 week and the hepatic responses were examined.

Result : Upon the administration of PFOA and PFDA, three peroxisome proliferator-responsive parameters, peroxisomal beta-oxidation, microsomal 1-acylglycerophospho-choline (1-acyl-GPC) acyltransferase and cytosolic long-chain acyl-CoA hydrolase, were induced in a dose-dependent manner. A multiple regression analysis of the three parameters revealed that the data from rats treated with PFOA and PFDA shared one common line, indicating a marked correlation among the inductions of the three parameters. The activities of glutathione (GSH) S-transferases towards 1-chloro-2,4-dinitrobenzene (CDNB) and 1,2-dichloro-4-nitrobenzene (DCNB) were depressed by PFOA and PFDA. Significant inverse correlations were found between activities of GSH S-transferases and peroxisomal beta-oxidation. The administration of PFOA and PFDA significantly increased hepatic concentration of triacylglycerol. The perfluorocarboxylic acids at relatively high doses caused accumulation of cholesterol in liver. Electron microscopic studies showed that the administration of PFOA and PFDA caused an increase in cell size and proliferations of peroxisomes, and that the treatment of rats with PFDA at dietary concentration of 0.01% caused a marked increase in small lipid droplet in hepatocytes, indicative of hepatotoxic manifestations. The present results suggest that when PFOA and PFDA are administered at low levels, there are no differences between the properties of the perfluorocarboxylic acids as peroxisome proliferators, although the administration of PFDA at the doses exceeding a certain level becomes markedly toxic to hepatocytes.

Test substance : PFOA

05.12.2005 (359)

Type	:	Sub-chronic
Species	:	rat
Sex	:	no data
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	0.01%
Control group	:	
Method	:	other
Year	:	1999
GLP	:	no data
Test substance	:	other TS

Method : The effects of PFOA feeding on hepatic levels of glycerolipids and the underlying mechanism were investigated in rats fed with 0.01% of PFOA in the diet for 1 week.

Result : Feeding of rats with 0.01% of PFOA in the diet for 1 week caused an increase in the contents of phosphatidylcholine (PtdCho), phosphatidylethanolamine (PtdEtn), phosphatidylinositol (PtdIns), phosphatidylserine (PtdSer) and triglyceride (TG), which were 2.2, 2.4, 2.4, 1.6 and 5.2 times over control, respectively, on the basis of whole liver. The activities of glycerol-3-phosphate acyltransferase, diacylglycerol kinase and PtdSer decarboxylase were significantly increased upon PFOA feeding, whereas the activities of CTP:phosphoethanolamine cytidylyltransferase and PtdEtn N-methyltransferase were decreased. On the other hand, the activity of CTP:phosphocholine cytidylyltransferase was not increased by PFOA. Upon PFOA feeding, hepatic level of 16:0-18:1 PtdCho was markedly increased and, by contrast, the levels of molecular species of PtdCho which contain 18:2 were decreased, resulting in the reduced concentration of molecular species of serum PtdCho containing 18:2. The increase in the level of hepatic 16:0-18:1 PtdCho seemed to be due to 3-fold increase in the activities of both delta9 desaturase and 1-acylglycero-phosphocholine (1-acyl-GPC) acyltransferase. The mechanism by which PFOA causes the accumulation of glycerolipids in liver was discussed.

Test substance : PFOA

05.12.2005 (396)

Type	:	Sub-chronic
Species	:	rat
Sex	:	no data
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	Daily
Frequency of treatm. Post	:	10 days
exposure period	:	
Doses	:	0.02%
Control group	:	
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	other TS

Method : Most effects of the peroxisome proliferator clofibrate on rat liver are marginal or absent in selenium (Se) deficiency. The purpose of the present study was to determine whether the uptake or distribution of clofibrate is altered by Se deficiency.

Result : Rats were fed a Se-adequate or Se-deficient diet for 10-11 weeks and then these same diets with 0.5% (w/w) clofibric acid (the direct acting hydrolysis product of clofibrate) or 0.02% (w/w) PFOA for 10 days. Other groups of rats received radiolabeled clofibrate by intubation. Clofibric acid was an

ineffective as clofibrate in producing effects (i.e. decreased body weight gain, increases in liver somatic index and protein content of the mitochondrial fraction, and increased activities of catalase and peroxisomal fatty acid beta-oxidation) in the liver of Se-deficient rats. Microsomal omega-hydroxylation was, however, equally induced in both dietary groups. In contrast to clofibric acid, the biological effects of PFOA were not affected by Se status. Furthermore, neither the tissue distribution (plasma, liver and kidney) nor the urinary excretion of 14C was affected by Se deficiency. These results demonstrate that the hydrolysis of clofibrate to clofibric acid is not impaired in the Se-deficient rat. In addition, the involvement of Se in the effects of peroxisome proliferators differs for different members of this structurally heterogeneous group of compounds. It is concluded that the Se-deficient rat may provide valuable information concerning the biochemical mechanism(s) underlying peroxisome proliferation.

Test substance : PFOA

05.12.2005 (488)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 2 weeks
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.01%
Control group :
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : To elucidate the relationship between peroxisome proliferation of perfluorinated compounds and oxidative DNA damage, PFOA, PFDA, perfluorobutyric acid (PFBA) and perfluorooctane (PFO) were administered to 6-week-old F-344 male rats.

Result : After a single intraperitoneal (i.p.) injection of PFOA, PFBA or PFO in corn oil at a dose of 100 mg/kg, significant increase of liver weight and 8-hydroxydeoxyguanosine (8-OH-dG) levels in liver DNA were observed in PFOA-treated rats. Oral administration of powdered diet containing 0.02% PFOA or 0.01% PFDA for 2 weeks resulted in significant increases of liver weight and 8-OH-dG levels in liver DNA in rats given both chemicals. On the other hand, no increase in 8-OH-dG levels in kidney DNA was found in either of the studies. Our results demonstrate that, as with other peroxisome proliferators (phthalic ester plasticizers and hypolipidemic drugs), PFOA and PFDA induced peroxisome proliferation.

Test substance : PFOA

05.12.2005 (586)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Fischer 344
Route of admin. : oral feed
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1992
GLP : no data

Test substance : other TS

Method : The relationship between hepatomegaly and the hepatocarcinogenesis associated with peroxisome proliferators was examined in male rats.

Result : Male F-344 rats were maintained on diets containing clofibrate, ciprofibrate, nafenopin, gemfibrozil, Wy-14,643, di(2-ethylhexyl)phthalate (DEHP), or di(2-ethylhexyl)adipate (DEHA) at carcinogenic doses for 1 week. A close correlation between relative liver weights and hepatocarcinogenicity was observed. Administration of perfluorooctanoic acid (PFOA), perfluorodecanoic acid (PFDA), simfibrate, or DL-040, for which hepatocarcinogenicity is not known, resulted in hepatomegaly in all treated groups, this being especially marked in the PFOA case. Therefore, PFOA may have strong hepatocarcinogenic potential. Administration of the antioxidants butylated hydroxyanisole (BHA) or vitamin E (VE) did not affect the hepatomegaly induced by DEHP. These results suggest that the hepatomegaly may be an early biomarker for prediction of the potential hepatocarcinogenicity of peroxisome proliferators. However, this requires further clarification in terms of its relation to the oxidative stress thought to be involved in peroxisome proliferator-induced hepatocarcinogenesis.

Test substance : PFOA

05.12.2005 (587)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain :
Route of admin. : oral feed
Exposure period : 2, 22, or 26 weeks
Frequency of treatm. Post : Daily
exposure period : 4 weeks
Doses : 0.01%
Control group :
Method : other
Year : 1990
GLP : no data
Test substance : other TS

Method : Male and female rats were fed on a diet containing 0.01% (w/w) PFOA for 2, 22, or 26 weeks and effect of PFOA on activities of microsomal 1-acylglycerophosphocholine acyltransferase, microsomal stearoyl-coenzyme A (CoA) desaturase, peroxisomal-oxidation and on acyl composition of microsomal phosphatidylcholine in liver were studied.

Result : The treatment of male rats with PFOA for 2 weeks caused increases in the activities of stearoyl-CoA desaturase, 1-acylglycerophosphocholine acyltransferase, and peroxisomal beta-oxidation. The elevated activities of microsomal 1-acylglycerophosphocholine acyltransferase and peroxisomal beta-oxidation were unchanging throughout the long-term treatment. The induced activity of microsomal 1-acylglycerophosphocholine acyltransferase was found to be highly correlated with the induced activity of peroxisomal beta-oxidation. In contrast to these two enzymes, the increased activity of stearoyl-CoA desaturase by the short-term treatment of rats with PFOA did not last for 26 weeks, although the activity in rats treated for the long-term was higher than that of age-matched controls. The treatment of male rats with PFOA caused great alterations in the acyl composition of microsomal phosphatidylcholine. The high correlation seen between proportion of 18:1 in the C-2 position of phosphatidylcholine and activities of both stearoyl-CoA desaturase and 1-acylglycerophosphocholine acyltransferase suggest that these two enzymes participate actively in the regulation of acyl composition of phosphatidylcholine in rat liver. The present results show that hepatic responses to PFOA remain consistent throughout the period of the administration, but the elevated activities of the hepatic enzymes and the

altered acyl composition of microsomal phosphatidylcholine returned to control levels within 4 weeks after PFOA was withdrawn from the diet. Even after the chronic administration of PFOA, these parameters of female rats responded only slightly to the challenges by the chemical, which indicates a marked sex-related difference being still apparent in the response of rat liver to PFOA.

Test substance : PFOA

05.12.2005 (607)

Type : Sub-chronic
Species : rat
Sex :
Strain :
Route of admin. : oral feed
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1995
GLP : no data
Test substance : other TS

Method : A number of structurally diverse chemicals cause peroxisome proliferation via unknown mechanisms(s). A common characteristic shared by these compounds is the presence of a carboxylic acid group in the structure, or biotransformation to metabolites containing such a group. The present study was undertaken to investigate whether activation of these carboxylic groups to thioesters is an important step in the mechanism of action of these chemicals.

Result : Treatment of control rats with PFOA increased hepatic peroxisomal beta-oxidation 4- to 5-fold to 34 mU/mg protein. Feeding pantothenic acid-free diet to male rats (40-50 g body wt) for 5 weeks reduced hepatic Coenzyme A (CoA) levels and PFOA-induced peroxisomal beta-oxidation by 40% and 30%, respectively. Restoration of hepatic CoA to normal levels by supplements of pantothenic acid (100 mg/kg/day for 7 days) restored PFOA-induced peroxisomal beta-oxidation to 34 mU/mg protein. It is concluded that CoA is an important factor in the process by which peroxisome proliferators exert their effect on the liver. Results support the hypothesis that peroxisome proliferator-thioester formation is critical for induction of peroxisomes.

Test substance : PFOA

05.12.2005 (652)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period :
Doses :
Control group :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Oxidative DNA damage has been implicated to be one of the important underlying mechanisms by non-mutagenic carcinogens. Meanwhile, 8-

hydroxydeoxyguanosine (8-OH-dG) is shown to be an appropriate parameter to detect the oxidative DNA damage both in vivo and in vitro. In this study, 8-OH-dG levels were measured in the liver and kidney DNA of male rats administered PFOA or PFDA in the diet for 2 weeks or by a single i.p. injection.

Result : PFOA and PFDA produced high levels of 8-OH-dG in liver DNA when administered in the diet or i.p. These results clearly indicate the increase of 8-OH-dG levels in the target organ DNA is closely related to the organ specificity of non-mutagenic carcinogens.

Test substance : PFOA

05.12.2005 (311)

Type : Sub-chronic
Species : rat
Sex : male
Strain : other: Crl:CD(SD)BR
Route of admin. : gavage
Exposure period : 1, 3, or 7 days
Frequency of treatm. Post : Daily
exposure period : None
Doses : 50 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO was dissolved in distilled water and administered orally by gavage for 1, 3, or 7 days with 50 mg APFO/kg. Control rats were dosed with distilled water.

Some rats received C14-labeled sodium acetate 24 hours after the last dose. The rats were killed after the last dose or 3 hours after the administration of radiolabeled sodium acetate, and the livers were removed for examination.

For the microsomal enzyme studies, livers from ether-anesthetized rats that had been dosed for 3 consecutive days were weighed and prepared for the assay.

Result : Biochemical and morphological changes associated with APFO-induced hepatomegaly were studied in rats. Liver weights were significantly increased in all APFO-treated rats. The relative amount of DNA/g of liver decreased; however, the total amount of hepatic DNA was not significantly affected. Cytochrome P-450 and benzphetamine-N-demethylase activity were significantly increased by APFO administration. Carnitine acetyltransferase and carnitine-palmitoyl-transferase activities were also significantly increased. Ethoxyresorufin-O-demethylase activity was decreased after one or three doses. Glutathione-S-transferase and uridine-diphosphoglucuronyl-transferase were not significantly affected by APFO administration. Incorporation of radiolabeled sodium acetate into hepatic lipids except for diacylglycerols, squalene, and sterols containing 27 carbon atoms was significantly increased by APFO administration. Proliferation of the endoplasmic reticulum, mitochondria, and peroxisomes was observed in treated rats. The hepatomegaly induced by APFO is due to hypertrophy rather than hyperplasia. Peroxisome proliferation does not necessarily result in hypolipidemia, as evidenced by the observed increase in lipogenesis in the treated rats.

Test condition : Control rats were pair-fed with the treated rats.

05.12.2005 (494)

Type : Sub-chronic
Species : rat

Sex	:	male
Strain	:	other: ChR-CD
Route of admin.	:	gavage
Exposure period	:	2 weeks
Frequency of treatm. Post	:	10 consecutive doses
exposure period	:	14 days
Doses	:	6.7 mg/kg
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1962
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Each of 6 rats received 10 daily doses of APFO by intragastric intubation as an aqueous solution. Body weights were recorded. Three rats were killed 4 hours after receiving the 10th dose, and the remainder were killed 14 days later. Organ weights were recorded. Six undosed rats served as controls.

Result : Administration of ten successive doses of 6.7 mg/kg to six rats caused moderate enlargement of the liver and slight enlargement of kidneys and testes. Simultaneously there was a slight depression of pancreatic weight and the lungs of rats showed slightly enhanced pneumonitis. At the end of the dosing regimen, the livers of the test rats were about 45% heavier than the average liver weight of the control rats. This change persisted after cessation of dosage, but the weight discrepancy was somewhat less since 14 days later the livers were only 20% heavier than those of the control rats.

Test condition : There were 6 male rats in the test and control group.

05.12.2005 (159)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: Crl:CD(SD)IGS BR
Route of admin.	:	gavage
Exposure period	:	5 or 10 days
Frequency of treatm. Post	:	Daily
exposure period	:	13, 24, 52, or 93/94 days
Doses	:	20 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	2000
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : The objective of this study was to evaluate the potential of APFO, when administered by gavage, to be absorbed and to accumulate in a mammalian system. Groups of 5 male Crl:CD (SD)IGS BR rats each were exposed to 20 mg/kg/day of APFO. The test substance was administered to one group of 5 rats for 5 consecutive days and to other groups of 5 rats for 10 days. Approximately 2 hours after the first dose, blood was collected from the orbital sinus of each rat from the 5-dose group. On selected days (5, 10, 13, 24, 52, 93/94) 5 rats per group were euthanized and the blood and livers were collected. Body weight and clinical signs were recorded on each day of dosing and then approximately every other week during the recovery period. Additionally, 2 negative controls, corn oil and corn oil/acetone (80:20), were tested as described above.

Result : Rats dosed with APFO exhibited wet perineum and diarrhea during the dosing period. Alopecia was observed during the recovery period. Liver weights were up to 75% higher than negative controls. By day 94, liver weights were similar in test and control rats.

05.12.2005 (206)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other: Crl:CD(SD)IGS BR
Route of admin.	:	gavage
Exposure period	:	20 days
Frequency of treatm. Post	:	Daily
exposure period	:	86 days
Doses	:	20 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	2001
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : The objective of this study is to compare the internal exposure to and biopersistence of PFOA in rats with test substances containing straight-chain APFO or a mixture of APFO isomers. The rat was selected for these comparisons because of its use in related toxicity studies and the oral route of exposure was selected because it is relevant for human health risk extrapolation. Internal exposure was determined by measuring plasma area-under-the-curve (AUC) of total PFOA. AUC, which is the integral of plasma PFOA concentration over time, is the most common means for expressing internal dose. Biopersistence was assessed by quantifying terminal elimination plasma half-life. A dosage of 20 mg/kg was selected for each test substance. This dosage was expected to produce less than a 10% difference in mean body weight over 20 days of exposure (when compared to vehicle control) for both test substances based on previously reported data.

Remark : Also included was the linear form of APFO.

Result : Groups of 5 male and 5 female rats were administered for 20 days, 20 mg/kg/day of either linear APFO or the linear and branched chain mixed isomers. Mild reductions in body weights and body weight gains (compared to the controls) were observed in both treated groups of male rats. While the magnitude of effect was similar in both test groups, a more complete recovery form these effects occurred in the males exposed to the linear form. Body weights in female rats were not affected. No compound-related deaths or clinical signs were seen in either group. No PFOA was detected in plasma collected prior to the start of the test. Kinetic analysis of PFOA plasma levels demonstrated no significant differences between the two test substances in plasma biopersistence. Terminal half-lives in male rats were 9.6 and 10.4 days for the linear and mixed isomers, respectively. Terminal half-lives were less than one day for females.

Test condition : The test and control groups were comprised of 5 male and 5 female rats each.

05.12.2005 (212)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: CD
Route of admin.	:	gavage
Exposure period	:	14 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	1, 10, 25, or 50 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1992
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : CD rats (15/group) were randomly assigned to receive either 0, 1, 10, 25, or 50 mg/kg of APFO. The rats were gavaged daily with the appropriate dose of APFO or vehicle (deionized water) for 14 consecutive days. In addition, a second control group was pair-fed to the 50 mg/kg dose group to control for the effects of inanition on the hormonal status of the animals. On test day 15, the rats sacrificed and blood was collected. Serum was stored until analyzed for testosterone, estradiol, and LH concentrations. The following absolute and relative organ weights were measured: liver, testes, epididymides, accessory sex organ unit including fluids but with bladder removed, ventral and dorsolateral prostate, coagulating glands, seminal vesicles with fluid removed, and levator ani muscle. The right testis was placed in Bouin's fixative and evaluated microscopically. The fixed testes were imbedded in paraffin, sectioned at 6 um, and stained with hematoxylin and eosin for histologic evaluation.

Challenge experiments, which can identify the presence and location of a lesion in an endocrine axis, were also undertaken to clarify the significance of this downward trend in serum testosterone following the administration of APFO. In this experiment, a group of rats was administered 50 mg/kg/day of APFO for 14 days. One hour before termination, rats received either a human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), or naloxone challenge. These rats were euthanized, blood was collected, and serum was prepared. Serum was analyzed for testosterone and LH concentrations. In addition, serum collected from the hCG-injected animals was also analyzed for progesterone, 17alpha-hydroxyprogesterone, and androstenedione concentrations.

Result : A dose-dependent decrease in body weight and relative accessory sex organ (ASO) weights was seen, with the relative ASO weights of the 50 mg/kg/day group significantly less than those of the pair-fed controls. Serum estradiol levels were elevated in the 10, 25, and 50 mg/kg/day groups. Estradiol levels in the 50 mg/kg/day group were 2.7-fold greater than those of the pair-fed controls. The increase in serum estradiol levels occurred at the same dose levels as the increase in hepatic beta-oxidation activity. A significant downward trend with dose was seen in serum testosterone levels when compared with the ad libitum controls. However, when the 50 mg/kg/day group was compared with their pair-fed controls, no significant differences were seen. Challenge experiments, which can identify the presence and location of a lesion in an endocrine axis, were undertaken to clarify the significance of this downward trend in serum testosterone following the administration of APFO. Following hCG challenge, serum testosterone levels in the 50 mg/kg/day group were significantly decreased by 50% from those of the ad libitum controls. Similar decreases, although not significant, were seen in serum testosterone following GnRH and naloxone administration to the 50 mg/kg/day APFO group.

Test condition : In the dose-response experiment, the test and control groups were comprised of 15 male rats each. In the challenge experiment, the test and control group was comprised of 30 male rats.

Conclusion : These studies suggest that the decrease in serum testosterone following APFO administration was due to a lesion at the level of the testis. Androstenedione levels in the APFO treated rats were decreased 60% from those in the ad libitum controls, suggesting the decrease in serum testosterone following hCG challenge may be due to a decrease in the conversion of 17-alpha-hydroxy-progesterone to androstenedione. The conclusion was that the elevated estradiol levels in the treated rats may be responsible for the decreased relative accessory sex organ weight and serum testosterone levels seen in this, study as well as the increased incidence of Leydig cell adenomas observed in a chronic, 2-year feeding study in rats administered APFO.

05.12.2005 (127)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: CD
Route of admin.	:	gavage
Exposure period	:	14 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	25 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1995
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : CD rats (15/group) were randomly assigned to 3 groups designated as either an ad libitum control, pair-fed control, or 25 mg/kg/day APFO groups. Ten rats per group were assigned to the in vivo study and 5 rats per group were assigned to the ex vivo study. The rats were gavaged daily with the appropriate dose of APFO or vehicle (deionized water) for 14 consecutive days. All rats were weighed daily and dose volumes were calculated from these weights. Individual food consumption was determined daily throughout the study. The pair-fed control group received the mean amount of food consumed by the APFO-treated rats from the previous day.

On test day 15, rats in the in vivo study were euthanized and blood was collected for serum preparation. Serum was analyzed for testosterone, estradiol, or testicular interstitial fluid transforming factor alpha (TGFa) concentrations. Liver, testes, and accessory sex organ unit (prostate, seminal vesicles with fluid, and coagulating glands) were weighed at necropsy and relative organ weights calculated. Testicular interstitial fluid was collected and analyzed for testosterone, estradiol, or TGFa concentrations.

On test day 15, rats in the ex vivo study were euthanized and blood was collected for serum preparation. Analyses were as described above. At the time of euthanasia, the Leydig cells were isolated and cultured as described for the in vivo study.

To evaluate the potential for APFO to induce aromatase activity, a separate in vivo experiment was performed wherein 5 pair-fed control and 5 25 mg/kg APFO rats were treated as described above. On test day 15, rats were euthanized and blood was collected for serum estradiol levels, and testes, accessory sex organ unit, epididymal fat pads, liver, and a sample of skeletal muscle from the thigh were weighed. With the exception of the accessory sex organ unit, microsomes were prepared from each tissue. These tissues were chosen because they are the major sources of aromatase activity in males. In addition, hepatic peroxisomes were prepared. Microsomal aromatase and peroxisomal beta-oxidation activities were determined.

Result : A decrease in body and accessory organ unit weights and an increase in liver weights was seen in the APFO group when compared with the ad libitum control. When the APFO group was compared to the pair-fed control group only the liver weight was increased. Although the serum testosterone concentration remained unchanged, the serum estradiol concentration was significantly higher in the APFO group than in the pair-fed control group. Testicular interstitial fluid estradiol concentrations were also significantly higher in the APFO group. In addition, testicular interstitial fluid transforming growth factor alpha levels were also increased, consistent with the hypothesis that estradiol may modulate growth factor expression within the testis. In a follow-up study, APFO produced a 4.5-

fold increase in hepatic aromatase when compared to the pair-fed control, but did not increase aromatase activity in the testis, muscle, or fat.

In ex vivo studies, Leydig cells were isolated from rats following 14 days of dosing. The hCG-stimulated Leydig cells from the APFO-treated rats had statistically greater increases in testosterone production than in controls. In contrast, cultured Leydig cells treated in vitro with APFO produced a dose-dependent decrease in testosterone and at 500 uM produced an increase in estradiol.

Test condition : The test and control groups were comprised of 15 male rats each.

05.12.2005 (92)

Type : Sub-chronic
Species : rat
Sex : male
Strain : other: Crl:CD BR (CD)
Route of admin. : gavage
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period : None
Doses : 0.2, 2, 20, or 40 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1996
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Six groups of 15 male rats were included in this study, 4 of which received 0.2, 2, 20, or 40 mg/kg/day of APFO. The study included 2 control groups which received the vehicle, deionized water. The ad libitum control was allowed free access to diet. Pair-fed control rats were fed the mean amount of diet consumed on the previous day by the rats dosed with 40 mg/kg of APFO. Individual food consumption was determined daily for all rats. All rats were dosed daily by gavage for 14 days using a dose volume of 2 mL/kg based on their individual daily body weight.

Rats were weighed on Test Day 15 and sacrificed and serum was prepared from the blood collected. The testes and liver were collected, weighed, and stored. Serum concentrations of estradiol were measured. beta-Oxidation activity in the hepatic peroxisome samples was determined as was aromatase activity and the microsomal concentration of total cytochrome P450.

Result : Treatment with APFO produced a dose-dependent decrease in body weight, and increases in absolute and relative liver weights, and in the protein yield of hepatic microsomes. These APFO-induced changes were associated with a 2-fold increase in the serum concentration of estradiol and up to a 16-fold increase in total hepatic aromatase activity. A significant linear correlation was established between serum estradiol and total hepatic aromatase activity.

The absolute weights and the aromatase activity of the testes were not affected by APFO. Hepatic peroxisomal beta-oxidation activity and the microsomal concentration of total cytochrome P450 were also increased by APFO. A comparison of estimated EC50 values suggested that these parameters may be less sensitive to induction by APFO than hepatic aromatase activity. Co-incubation of control liver microsomes with APFO in the aromatase assay for 2 hours dose dependently reduced the apparent aromatase activity. This inhibition of aromatase in vitro but increase in vivo was further investigated using cultured rat hepatocytes. Decreases in aromatase activity were found after up to 42 hours of treatment with APFO, but the enzyme activity was increased almost 2-fold after 66 hours.

Test condition : A pair-fed control group was included in addition to an ad libitum control

group. The test and control groups were comprised of 15 male rats each.

Conclusion : The results of this study suggest that the increased serum concentration of estradiol produced by APFO in rats is at least partly due to a direct effect on the liver to increase synthesis of estradiol through induction of aromatase cytochrome P450 in the endoplasmic reticulum.

05.12.2005 (419)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain :
Route of admin. : gavage
Exposure period : 3 days
Frequency of treatm. : Daily
Post exposure period : 1 day
Doses : 50, 100, or 150 mg/kg
Control group : no data specified
Method : other
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Male and female rats (225-250 g) were dosed by gavage at 50, 100, or 150 mg/kg for 3 consecutive days and were sacrificed on the fourth day.

Result : APFO caused a significant increase in liver weight in males but not females. The liver weight increase and hepatic histopathology in males was characteristic of a liver of an animal pretreated with phenobarbitol. Measurement of hepatic cytochrome P-450 levels revealed a two-fold increase in P-450 concentration in males, paralleled by a proportional increase in benzphetamine N-demethylase activity but no change in benzo[a]pyrene 3-hydroxylase activity. Female rats appeared to be resistant to the hepatic enlargement and cytochrome P-450 effects of APFO. These results indicate a preferential increase in the phenobarbital-type P-450 and explain, in part, the hepatomegaly observed in male rats dosed with APFO. The male-female difference in sensitivity is probably due to differences in metabolism and excretion.

09.12.2005 (491)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : gavage
Exposure period : 28 days
Frequency of treatm. : Daily
Post exposure period :
Doses : 3, 10, and 30 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1986
GLP : no data
Test substance : other TS

Method : PFOA was administered orally for 28 consecutive days. Another 12 animals (controls) received 0.5 mL/100 g saline each day. Animal behavior, body weight, as well as, water and food consumption were observed. Blood, urine, and some viscera were collected for the analysis of PFOA and histopathology.

Result : Food consumption decreased with increasing dose of PFOA. Serum PFOA concentrations were 6-19 times higher in the males than in the females (range 48.6-83.0 ug/mL males, and 2.4-11.2 ug/mL females). On the 7th day the mean PFOA excretion in the low dose group for the males was 157

ug/24 hours and 255 ug/24 hours for females. In the high dose group the corresponding figures were 2476 ug/24 hours (males) and 2917 ug/24 hours (females). On the 28th day the PFOA excretion for the low dose males was 609 ug/24 hours, 671 ug/24 hours for the females. In the high dose group the figures were 4619 ug/24 hours (males) and 4379 ug/24 hours (females).

Test substance : PFOA

05.12.2005 (382)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 21 days
Frequency of treatm. Post : Daily
exposure period :
Doses : 1, 3, 5, 10, or 15 mg/kg/day
Control group :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Microarray techniques of gene expression is an approach for exploring the biological effects of chemicals. Here, the Affymetrix, Inc. rat genome 230 2.0 GeneChip was used to identify alterations in gene regulation in Sprague-Dawley rats treated with five different concentrations of PFOA. Male rats were exposed by daily gavage to 1, 3, 5, 10, or 15 mg PFOA/kg bw for 21 days and at the end of the exposure, liver was isolated and total liver RNA were used for the gene chip analysis.

Result : Over 500 genes, whose expression was significantly altered by PFOA at two-fold changes compared to control, were examined. The effects were dose-dependent with exposure to 10 mg/kg causing alteration in expression of the greatest number of genes (over 800). Approximately 106 genes and 38 genes were consistently up- or down-regulated, respectively in all treatment groups. The largest categories of induced genes were those involved in transport and metabolism of lipids, particularly fatty acids. Other induced genes were involved in cell communication, adhesion, growth, apoptosis, hormone regulatory pathways, proteolysis and peptidolysis and signal transduction. The genes expression of which was suppressed were related to transport of lipids, inflammation and immunity, and especially cell adhesion. Several other genes involved in apoptosis; regulation of hormones; metabolism; and G-protein coupled receptor protein signaling pathways were significantly suppressed.

Test substance : PFOA

05.12.2005 (290)

Type : Sub-chronic
Species : rat
Sex : male
Strain : other: ChR-CD
Route of admin. : dermal
Exposure period : 2 weeks
Frequency of treatm. Post : 6 hours a day, 5 days a week
exposure period : 42 days
Doses : 20, 200, or 2000 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Male rats (age 8 weeks, weighing 210-245 g) were collared to prevent ingestion of the compound when preening and grooming during the 2-week exposure period. APFO, as an aqueous paste, was applied to the backs of each rat that had been shaved free of hair. Daily 6-hour exposures ended when the compound was wiped from the rats' backs with a gauze pad. Collars were removed after exposure day 10. Throughout the test period, food and water were available ad libitum. Body weights and clinical signs were recorded. After exposure day 10 and on recovery days 14 and 42, blood was taken from 5 rats from each group for hematology measurements. Gross necropsy and histopathological examinations were performed on 5 rats/group after exposure 10, and on recovery days 14 and 42. Mean absolute and relative organ to body weight analyses were performed. After exposure 10 and on recovery days 14 and 42, blood was collected from 5 rats/group for organo-fluorine determinations. Eye examinations were performed on each rat after exposure 9, and on recovery days 13 and 41. The procedure included gross observation of the eyes using a bright light, and semimicroscopic observation using a hand magnifying lamp and a slit-lamp biomicroscope. Data were analyzed by appropriate statistical methods.

Result : At 200 or 2000 mg/kg rats lost weight during the exposure period and showed slight reddening of the skin. Salivation was noted at 2000 mg/kg. Dose-related increases were noted in enzymes monitoring liver function. Liver damage was found in all groups following the tenth dose. During treatment there was an increase in liver weight. Coagulative necrosis of the epidermis at the dose site was noted in two rats dosed at 2000 mg/kg after ten days. Blood organo fluoride levels were elevated on the tenth day of exposure. These decreased during a 14 to 42 day recovery period.

Test condition : The control group was exposed to distilled water only.

There were 15 male rats in the test and control groups.

The test compound was wiped off after the 6-hour test period.

The exposure period was followed by a 42-day recovery period. Five rats per group were randomly selected for sacrifice on exposure day 10, and recovery days 14 and 42.

05.12.2005 (168) (371)

Type : Sub-chronic
Species : rat
Sex : male
Strain :
Route of admin. : oral unspecified
Exposure period : 5 days
Frequency of treatm. Post :
exposure period :
Doses : 25 mg/kg/day
Control group :
Method : other
Year : 1993
GLP : no data
Test substance : other TS

Method : Differences in the ability of metabolically-inert peroxisome proliferators PFDA, PFOA, perfluorooctane sulfonic acid (PFOS, C8) and 1-H,1-H-pentadecafluoro-n-octanol (PFOL, C8)) to induce three forms of hepatic microsomal carboxylesterase (RL1, RL2 and RH1) in the male rat were studied by measuring changes in hydrolytic activities towards p-nitrophenyl acetate (PNPA), isocarboxazid (ISOC) and butanilicaine (BUTA), which are thought to be specific substrates for RL1, RL2 and RH1, respectively, and by evaluating changes in the contents of the three isozymes by radial

immunodiffusion assay with specific antibodies.

Result : The administration of PFDA decreases PNPA hydrolase activity and RL1 content. On the other hand, PFOA (25 mg/kg/day for 5 consecutive days), PFOS and PFOL markedly increase all three hydrolase activities and the content of all three isozymes (except RH1 in the case of PFOA, where the increase was not statistically significant). The correlations between hydrolase activities and isozyme contents supported specificity of the three substrates, with the exception that the content of the predominant isozyme, RL2, showed a higher correlation with BUTA hydrolase activity than with ISOC hydrolase activity.

In conclusion, it was demonstrated that metabolically-inert perfluorinated fatty acids induce hepatic microsomal carboxylesterase isozymes, as determined by radial immunodiffusion analysis using specific antibodies.

Test substance : PFOA

05.12.2005 (327)

Type : Sub-chronic
Species : rat
Sex :
Strain :
Route of admin. : oral unspecified
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period :
Doses :
Control group :
Method : other
Year : 1989
GLP : no data
Test substance : other TS

Method : Rats were treated for 5 to 14 days with perfluoroacetate, perfluorobutyrate and perfluorooctanoate. Alterations in hepatic morphology with special reference to the peroxisomal compartment were investigated by light and electron microscopy following cytochemical staining of catalase activity with the alkaline 3,3'-diaminobenzidine medium.

Result : All three compounds induced hepatomegaly and peroxisome proliferation. Perfluorobutyrate and perfluorooctanoate were found to be more active than perfluoroacetate. Perfluorooctanoate-induced peroxisome proliferation was more prevalent in centrilobular than in periportal hepatocytes. Peroxisomes in centrilobular liver cells frequently were of round shape, exhibited diameters of up to 1.5 microns and were predominantly located within smooth endoplasmic reticulum-glycogen areas. In periportal cells, however, clusters of polymorphous peroxisomes ranging from 250 to 1,100 nm in diameter were observed at the periphery of smooth endoplasmic reticulum-glycogen regions. Peroxisome proliferation was accompanied by a change of peroxisomal and mitochondrial enzyme activities, in particular an increase in peroxisomal palmitoyl-CoA oxidation. Significant alterations in the concentration of peroxisomal matrix and membrane polypeptides were also noted. Within the first 2 days, perfluorooctanoate treatment exerted a strong hypolipidemic activity and both compounds perfluorooctanoate and perfluorobutyrate raised the level of hepatic free acid-soluble CoA nearly 10-fold as compared with control livers. The results suggest perfluorinated carboxylic acids to be model substances suitable to correlate biochemical and morphological parameters with the zonal heterogeneity of the peroxisomal compartment in rat liver.

Test substance : PFOA

05.12.2005 (344)

Type : Sub-chronic
Species : rat

Sex	:	
Strain	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	
Control group	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	other TS

Method : Induction of microsomal 1-acyl-glycerophosphocholine (GPC) acyltransferase in rat tissues by four peroxisome proliferators, clofibric acid, tiadenol, DEHP and PFOA, was examined.

Result : Among the nine tissues examined, kidney, liver and intestinal mucosa responded to the challenges by the peroxisome proliferators to induce the enzyme. The treatment of rats with various dose of clofibric acid, tiadenol, DEHP or PFOA resulted in an induction of kidney microsomal 1-acyl-GPC acyltransferase in a dose-dependent manner. Despite the structural dissimilarity of peroxisome proliferators, the induction of microsomal 1-acyl-GPC acyltransferase was highly correlated with the induction of peroxisomal beta-oxidation. The activity of microsomal 1-acyl-GPC acyltransferase was not affected by changes in hormonal (adrenalectomy, diabetes, hyperthyroidism and hypothyroidism) and nutritional (starvation, starvation- refeeding, fat-free-diet feeding and high-fat-diet feeding) states. The induction of renal microsomal 1-acyl-GPC acyltransferase was seen in mice subsequent to the administration of clofibric acid and tiadenol and in guinea pigs subsequent to the administration of tiadenol. These results may indicate that kidney microsomal 1-acyl-GPC acyltransferase is a highly specific parameter responsive to the challenges by peroxisome proliferators and may suggest that the possibility that the inductions by peroxisome proliferators of microsomal 1-acyl-GPC acyltransferase and peroxisomal beta-oxidation in kidney are co-regulated.

Test substance : PFOA

05.12.2005 (360)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	
Route of admin.	:	oral unspecified
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	
Control group	:	
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	other TS

Method : Inductions by perfluorooctanoic acid (PFOA) of hepatomegaly, peroxisomal beta-oxidation, microsomal 1-acylglycerophosphocholine acyltransferase and cytosolic long-chain acyl-CoA hydrolase were compared in liver between male and female rats.

Result : Marked induction of these four parameters were seen concurrently in liver of male rats, whereas the induction in liver of female rats were far less pronounced. The sex-related difference in the response of rat liver to PFOA was much more marked than that seen with clofibric acid or tiadenol. Hormonal manipulations revealed that this sex-related difference in the

induction is strongly dependent on sex hormones, namely that testosterone is necessary for the induction, whereas estradiol prevented the induction by PFOA.

Test substance : PFOA

05.12.2005 (363)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1989
GLP : no data
Test substance : other TS

Method : The effects of the peroxisome proliferators clofibric acid, tiadenol, and PFOA) on hepatic stearoyl-CoA desaturation in male and female rats were compared.

Result : Treatment of male rats with the three peroxisome proliferators increased markedly the activity of stearoyl-CoA desaturase. Administration of clofibric acid or tiadenol to female rats increased greatly the hepatic activity of stearoyl-CoA desaturase, the extent of the increases being slightly less pronounced than those of male rats. In contrast with the other two peroxisome proliferators, however, PFOA did not change the activity of stearoyl-CoA desaturase in female rats. Hormonal manipulations revealed that this sex-related difference in the effect of PFOA on stearoyl-CoA desaturase activity is strongly dependent on testosterone. The increase in stearoyl-CoA desaturase activity by peroxisome proliferators was not accompanied by any notable increases in the microsomal content of cytochrome b5 or the activity of NADH: cytochrome b5 reductase. The administration of the peroxisome proliferators greatly altered the acyl composition of hepatic phosphatidylcholine and phosphatidylethanolamine (namely the proportions of C18:1 and C20:3,n-9 fatty acids increased in both phospholipids), and the alterations were partially associated with the increase in stearoyl-CoA desaturase activity.

Test substance : PFOA

05.12.2005 (364)

Type : Sub-chronic
Species : rat
Sex : male
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1989
GLP : no data
Test substance : other TS

Method : The effect of clofibric acid, di(2-ethylhexyl)phthalate or PFOA to the liver of male rats was determined.

Result : Administration of clofibric acid,

di(2-ethylhexyl)phthalate or PFOA to male rats increased markedly microsomal 1-acylglycerophosphocholine (a-acyl-GPC) acyltransferase in a dose-dependent manner in liver. Simultaneous administration of actinomycin D or cycloheximide completely abolished the increase in the enzyme activity. The treatment of rats with clofibric acid did not affect the rate of decay of 1-acyl-GPC acyltransferase. Regardless of a great difference in the chemical structures of the peroxisome proliferators, high correlation was observed between the induced activities of microsomal 1-acyl-GPC acyltransferase and peroxisomal beta-oxidation. Stearoyl-CoA desaturase was induced by peroxisome proliferators in a dose-dependent manner; nevertheless, high correlation was not seen between the induced activities of desaturase and peroxisomal beta-oxidation. Hormonal (adrenalectomy, diabetes, hyperthyroidism and hypothyroidism) and nutritional (starvation, starvation-refeeding, fat-free diet feeding and high-fat diet feeding) alterations hardly affected the activity of 1-acyl-GPC acyltransferase. The present results indicate that microsomal 1-acyl-GPC acyltransferase is a useful parameter responsive to the challenges by peroxisome proliferators and suggest that a similar regulatory mechanism operates for the inductions of microsomal 1-acyl-GPC acyltransferase and peroxisomal beta-oxidation.

Test substance : PFOA
05.12.2005 (358)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : Response of rat kidney to the challenges by PFOA was studied using microsomal 1-acyglycerophosphocholine (1-acyl-GPC) acyltransferase as a parameter.

Result : Marked induction of the enzyme was brought about in kidney of male rats, whereas the induction in kidney of female rats was far less pronounced. The sex-related difference in the response of kidney to PFOA was much more marked than those seen with clofibric acid or tiadenol. Hormonal manipulations revealed that the sex-related difference in the response of kidney to PFOA was strongly dependent on the state of gonadal hormones of rats. After a prolonged administration of PFOA for up to 26 weeks, this sex-related difference was still evident. Induction of peroxisomal beta-oxidation was brought about concurrently with microsomal 1-acyl-GPC acyltransferase and a high correlation was confirmed between the inductions of these two parameters.

Test substance : PFOA
05.12.2005 (361)

Type : Sub-chronic
Species : rat
Sex : male
Strain :
Route of admin. :
Exposure period : 10 days
Frequency of treatm. :

Post exposure period	:	
Doses	:	0.5%
Control group	:	
Method	:	other
Year	:	1997
GLP	:	no data
Test substance	:	other TS
Method	:	The objectives of the present work were to study the effects of certain peroxisome proliferators on xenobiotic-metabolizing enzyme activities in the testes of normal and hypothyroid rats, i.e. phenol sulfotransferases (pST), phenol UDP-glucuronosyl transferases (pUDPGT), glutathione transferases (GST), catalase, epoxide hydrolase (EH), glutathione peroxidase (GPX) and NAD(P)H quinone oxidoreductase (QR). Adult male rats (normal and hypothyroid) were treated for 10 days with clofibrate (0.5%), PFOA (0.5%), acetylsalicylic acid (1%, ASA) and di(2-ethylhexyl)phthalate (2%, DEHP) in their diet.
Result	:	Treatment of normal rats with peroxisome proliferators dramatically affects the activities of xenobiotic-metabolizing enzymes (40-60% reduction). The highest effects are seen in catalase activity (50-60% with PFOA and ASA), pUDPGT (55% with PFOA), pST (55% with PFOA) and QR (50% with DEHP). These effects are not seen or are weaker after induction of hypothyroidism. Taken together, it is concluded that different classes of peroxisome proliferators have different effects on rat testicular xenobiotic-metabolizing enzymes.
Test substance	:	PFOA

05.12.2005 (438)

Type	:	Sub-chronic
Species	:	rat
Sex	:	no data
Strain	:	
Route of admin.	:	oral unspecified
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	
Control group	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	other TS
Method	:	The relative contribution of stearoyl-CoA desaturase and 1-acylglycerophosphocholine (1-acyl-GPC) acyltransferase, which are induced by peroxisome proliferators, to the increase in the proportion of oleic acid in C-2 position of phosphatidylcholine (PtdCho) in the liver of rats was investigated. Rats were administered either clofibric acid, tiadenol) or PFOA in varying doses.
Result	:	The proportion of oleic acid in C-2 position of PtdCho in hepatic microsomes was increased in commensurate with the increase in activities of stearoyl-CoA desaturase and 1-acyl-GPC acyltransferase. Multiple regression analysis revealed that although there is a high correlation among the three parameters examined, the partial correlation between the proportion of oleic acid in the C-2 position and the activity of stearoyl-CoA desaturase is significantly higher than that between the proportion of oleic acid in the C-2 position and the activity of 1-acyl-GPC acyltransferase. The contribution of stearoyl-CoA desaturase to the increase in the proportion of oleic acid in the C-2 position thus appears greater than that of 1-acyl-GPC acyltransferase.
Test substance	:	PFOA

05.12.2005 (442)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	
Route of admin.	:	oral unspecified
Exposure period	:	3 days
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	50 mg/kg/day
Control group	:	
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	other TS
Method	:	PFOA causes liver enlargement (hepatomegaly) in rats. These studies were undertaken to examine the morphological and biochemical basis of PFOA-induced hepatomegaly. Male rats were dosed orally with 50 mg/kg/day of PFOA for 3 days.
Result	:	Hepatocytes were enlarged, occluded sinusoidal spaces, and contained more mitochondria and microbodies (peroxisomes). Biochemically, the concentration of cytochrome P-450 was increased more than 3-fold together with a 2-fold increase in benzphetamine N-demethylase activity. Carnitine acetyl-transferase (CAT), a marker enzyme for both mitochondria and peroxisomes, was elevated 12-fold and carnitine palmitoyltransferase (CPT), a marker enzyme for mitochondria, was elevated 2-fold. The incorporation of [14C]-acetate into hepatic phospholipids, triacylglycerols, and cholesterol esters was also increased. Plasma total cholesterol and triacylglycerols were unaffected. Thus, the factors underlying PFOA-induced hepatomegaly are proliferation of the smooth endoplasmic reticulum, mitochondria, and to the greatest extent, peroxisomes. However, unlike peroxisome proliferating compounds reported thus far, PFOA is not hypolipidemic. Thus PFOA may be considered as a novel peroxisome proliferating agent.
Test substance	:	PFOA

05.12.2005 (493)

Type	:	Sub-chronic
Species	:	rat
Sex	:	no data
Strain	:	
Route of admin.	:	oral unspecified
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	
Control group	:	
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	other TS
Method	:	Previously we found a depression in the activity of hepatic xanthine dehydrogenase in rats fed clofibrate or di(2-ethylhexyl)phthalate. The present study further demonstrated that dietary addition of other peroxisome proliferators, including bezafibrate, dehydroepiandrosterone and PFOA also depressed activity of hepatic xanthine dehydrogenase in rats.
Result	:	Western and Northern blot analyses indicated the depression in hepatic xanthine dehydrogenase protein and mRNA by feeding bezafibrate. These results suggest that administration of a wide variety of peroxisome

proliferators depresses the activity of hepatic xanthine dehydrogenase in rats and that the depression in activity of this enzyme by the proliferator might be mediated by decreased mRNA of the enzyme. Further, nuclear run-on analysis revealed no influence of feeding bezafibrate on the transcriptional activity of hepatic xanthine dehydrogenase gene, suggesting increased degradation of the enzyme mRNA by the chemical.

Test substance : PFOA

05.12.2005 (540)

Type : Sub-chronic
Species : rat
Sex : male
Strain : Wistar
Route of admin. : s.c.
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : The possibility of using cytosolic long-chain acyl-CoA as a parameter to measure the response of liver to peroxisome proliferators was studied.

Result : A subcutaneous injection of perfluorooctanoic acid (PFOA) to male Wistar rats caused an increase in activity of cytosolic long-chain acyl-CoA hydrolase. This increase in activity seems to be due to enzyme induction, since it was prevented by simultaneous administration of cycloheximide or actinomycin D with PFOA. The activity of cytosolic long-chain acyl-CoA hydrolase was increased in a dose-dependent manner by the administration of three peroxisome proliferators with diverse chemical structures: clofibric acid, tiadenol, and PFOA. The increased activity produced by clofibric acid lasted throughout a 22-week treatment. A good correlation was found between the activities of cytosolic long-chain acyl-CoA hydrolase and peroxisomal beta-oxidation induced by the administration of the peroxisome proliferators. These results indicate that cytosolic long-chain acyl-CoA hydrolase is a suitable parameter for measuring the response of rat liver to challenges by peroxisome proliferators.

Test substance : PFOA

05.12.2005 (357)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : i.p.
Exposure period : 1 week
Frequency of treatm. Post : Daily
exposure period :
Doses : 20 mg/kg
Control group :
Method : other
Year : 1990
GLP : no data
Test substance : other TS

Method : The effects of PFOA on hepatic peroxisomal oxidation and carnitine-acetyltransferase (CAT) were investigated in rats and mice. Wistar-rats and ddY-mice were injected intraperitoneally (ip) with 0 to 20 mg/kg PFOA daily

for 1 week. Wistar-rats were administered 0 or 0.01% PFOA in their diet for 2 or 26 weeks. At the end of each treatment the animals were killed and the livers were removed and weighed. The post nuclear supernatants were prepared and assayed for peroxisomal-beta-oxidase (PBO) and CAT.

Result : PFOA after ip injection, caused a significant dose-dependent hepatomegaly in male rats and mice of both sexes. PFOA caused a significant dose-related induction of PBO and CAT activity in male rats and male and female mice. PFOA at 10 and 20 mg/kg caused a slight decrease in PBO and CAT activity in female rats. In the feeding investigation PFOA significantly increased PBO and CAT activity in male rats at both time points. CAT activity was significantly increased in female rats at both times. PFOA increased PBO activity in female rats only in the 26 week investigation. The authors conclude that the observed species and sex related differences in the hepatic biochemical response to PFOA indicate that when extrapolating hazards of perfluorocarboxylic-acids to humans from data obtained in animal experiments biochemical information should be included in the risk assessment.

Test substance : PFOA

05.12.2005 (606)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period : None
Doses : 1, 3, 10, 30, 100, or 300 ppm
Control group : yes, concurrent no treatment
Method : other
Year : 2001
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 5 male and 5 female CD-1 mice were exposed for 14 days to control diet (0 ppm) or diet containing 1, 3, 10, 30, or 300 ppm of either linear APFO or the linear and branched chain mixed isomers. Body weights, food consumption, and clinical observations were evaluated weekly. After the 14-day exposure period, all non-fasted mice were sacrificed and their livers were removed and weighed.

Remark : Also included was a linear form of APFO.

Result : There were no compound-related deaths or clinical signs of toxicity. Overall body weight loss was observed in male mice fed 100 or 300 ppm of either form of APFO. Body weight losses were also observed in female mice fed 100 or 300 ppm of linear APFO or 300 ppm of the mixed form. Compound-related reductions (compared to controls) in body weights and body weight gains were also observed in male mice administered 30 ppm of the linear form. Both forms produced compound-related increases in liver weights compared to controls. In male mice, liver weight increases were seen in all groups fed either form of APFO. In female mice, liver weight increases were seen in groups fed 3 ppm or more of either form of APFO.

Test condition : The test and control groups were comprised of 5 male and 5 female mice each.

05.12.2005 (211)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed

Exposure period	:	14 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	30 ppm
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Male and female mice (age 44 days, weighing 24 to 35 g) were fed diets containing either APFO, PFDA, or mixtures of the two test substances for 14 consecutive days. Male and female controls were observed concurrently and fed only ground chow. Individual body weights and clinical signs were recorded. Liver weights were recorded at the 14-day sacrifice. Male and female CD-1 mice were fed either PFDA at dose levels of either 3, 10, 30, 300, or 3000 ppm, or APFO at 30 ppm or the 2 test materials combined for a total of 30 ppm (15 ppm each or 25 ppm and 5 ppm each) for 14 consecutive days.

Result : All the mice fed 300 or 3000 ppm of PFDA died within 12 days.

Liver weight/body weight ratios showed an increase at all levels tested when compared to controls. Mixing the 2 test materials and feeding at 30 ppm did not alter the effects. The materials appear to have similar potentials for causing liver enlargement in mice. Liver enlargement appears to be dose-related with PFDA being the more toxic of the two materials tested.

05.12.2005 (187)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	14 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	30, 300, or 3000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Male and female mice (age 43 and 44 days, weighing 21 to 38 g) were fed diets containing either 30, 300, or 3000 ppm APFO for 14 consecutive days. Male and female controls were observed concurrently and fed only ground chow. Individual body weights, food consumption, and clinical signs were recorded. Liver weights were recorded at the 14-day sacrifice.

Result : All the mice fed 3000 ppm of APFO died. Deaths also occurred at 300 ppm. Body weight loss was indicated at 300 and 3000 ppm. Liver weight/body weight ratios showed a sharp increase over controls in the mice fed the 30 ppm APFO diet. Dose-response increases were seen. Clinical signs observed for APFO also included unkempt head area and weakness.

Test condition : The test and control groups were comprised of 5 male and 5 female mice each.

05.12.2005 (184) (372)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female

Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	14 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	10, 30, 100, 300, 1000, 3000, or 10,000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1981
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 10 male and 10 female mice (age 41 and 42 days, weighing 19 to 30 g) were fed a diet containing 10, 30, 100, 300, 1000, 3000 or 10,000 ppm of APFO for 14 days. Male and female controls were observed concurrently and fed only ground chow. Individual body weights, food consumption, and clinical signs were recorded. Liver weights were recorded at the 14-day sacrifice.

Result : Deaths occurred in the 1000, 3000 and 10,000 ppm groups. Body weight loss was indicated at the end of each week at 300 ppm and more. Liver weight/body weight ratios showed an increase at 10 ppm and were dose-dependent. Clinical signs of toxicity included weakness, tremors, piloerection, pallor, stained perineal area and unkempt appearance.

05.12.2005 (176)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	3 weeks
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	0.01, 0.03, 0.1, 0.3, 1, 3, 10, or 30 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	= 1 ppm
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 5 male and 5 female mice (age 41 and 42 days, weighing 21 to 33 g) were fed a diet containing 0.01, 0.03, 0.1, 0.3, 1.0, 3, 10 or 30 ppm of APFO (suspended in 1% corn oil before being mixed in ground chow) for 21 days. Male and female controls were observed concurrently and fed only ground chow. Individual body weights and clinical signs were recorded. Liver weights were recorded at the 21-day sacrifice.

Result : Livers were significantly heavier at 30 ppm, slightly heavier at 3 ppm and appeared normal at 10 ppm. No changes in liver weight were seen in the groups fed 1 ppm or less of APFO. The only clinical sign observed was sporadic weight loss.

05.12.2005 (185) (372)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	other: Charles River CD albino mice
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	30, 100, 300, 1000, 3000, 10,000, or 30,000 ppm

Control group : yes, concurrent no treatment
Method : other
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : In a 28-day study of Charles River-CD albino mice, 8 randomly assigned groups of 5 males and 5 females each were studied. After mice were allowed to acclimate for 8 days in individual cages they then received similar feed containing 30, 100, 300, 1000, 3000, 10,000, or 30,000 ppm of APFO for 28 days. The animals were observed daily and body weights and food consumption were recorded weekly. Animals that died during the study were examined for gross pathology, as were surviving animals at 28 days. It is stated the study included a complete examination of gross pathology and a representative set of tissues and organs were examined, but the specific list is not supplied. Livers were weighed to determine relative organ weight then stained for histopathologic examination.

Result : All animals in the 1000 ppm and higher groups died before the end of day 9. The entire 300 ppm group died within 26 days except one male. One animal in each of the 30 and 100 ppm groups died. Clinical signs were observed in mice exposed to 100 ppm and higher doses of PFOA. At 100 ppm some animals exhibited cyanosis on days 10 and 11 of testing, but appeared normal throughout the rest of the study. Animals fed 300 ppm exhibited roughed fur and muscular weakness as well as signs of cyanosis after 9 days of treatment. Animals fed 1000 ppm exhibited similar effects after 6 days and those receiving 3000 ppm or greater doses exhibited effects after 4 days. All mice fed APFO lost weight. Reductions in body weight gain were followed by weight losses in mice fed 30, 100, or 300 ppm. A dose-related pattern was seen in the depressed body weights. Relative and absolute liver weights were increased in mice fed 30 ppm or more APFO. Gross pathological examination of kidneys or other organs besides livers is not discussed. Treatment-related changes were observed in the livers among all APFO treated animals including enlargement and/or discoloration of 1 or more liver lobes. Histopathologic examination of all APFO treated mice revealed diffuse cytoplasmic enlargement of hepatocytes throughout the liver (pan lobular hypertrophy) accompanied by focal to multifocal cytoplasmic vacuoles. Degeneration and /or necrosis of hepatocytes and focal bile duct proliferation were also noted in mice within all groups.

Test condition : The test and control groups were comprised of 5 male and 5 female mice each.

05.12.2005 (332)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : C57BL
Route of admin. : oral feed
Exposure period : 2 weeks
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1995
GLP : no data
Test substance : other TS

Method : The peroxisome proliferators PFOA; 0.02% w/w), PFDA; 0.02%, w/w), nafenopin (0.125%, w/w), clofibrate (0.5%, w/w), and acetylsalicylic acid (ASA; 1%, w/w) were administered to male C57 BL/6 mice in their diet for two weeks. Parameters for Fe3+ ADP, NADPH or ascorbic acid-initiated

lipid peroxidation in vitro were measured.

Result : Approximately a two-fold increase in susceptibility to lipid peroxidation was obtained for all the peroxisome proliferators tested. Co-treatment of mice with the peroxisome proliferator ASA (1%, w/w) and a catalase inhibitor, 3-amino-1,2,4-triazole (AT; 0.4%, w/w) for 7 days resulted in little inhibition of peroxisome proliferation, an elevated level of H2O2 in vivo, and total inhibition of the increased susceptibility to lipid peroxidation in vitro. No increase in lipid peroxidation in vivo was observed. Certain antioxidant enzymes (DT-diaphorase, superoxide dismutase, glutathione transferase, glutathione peroxidase, and glutathione reductase) and components (ubiquinone and alpha-tocopherol) were also measured. The results showed that there was some induction of these antioxidant enzymes and components by ASA or aminotriazole, except for glutathione peroxidase and superoxide dismutase, which were inhibited. The possible involvement of oxidative stress in the carcinogenicity of peroxisome proliferators is discussed.

Test substance : PFOA

05.12.2005 (112)

Type : Sub-chronic
Species : mouse
Sex : male
Strain :
Route of admin. : oral feed
Exposure period : 2 to 10 days
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.02 and 0.1%
Control group :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : Male mice were exposed via their diet to perfluoro fatty acids of various chain-lengths (2-10 carbon atoms) at different doses (0.02 and 0.1% weight) and for different periods of time (2-10 days). Monitored were the effects on liver and body weights and a number of hepatic parameters, including mitochondrial protein content, microsomal contents of cytochromes P450 and b5, NADPH-cytochrome P450 reductase activity [measured as NADPH-cytochrome c reductase (EC 1.6.2.3)], microsomal and cytosolic epoxide hydrolase (EC 3.3.2.3) activities, cytosolic DT-diaphorase (EC 1.6.99.2), glutathione transferase (EC 2.5.1.18), glutathione peroxidase (EC 1.11.1.9) and superoxide dismutase (EC 1.15.1.1) activities, and levels of thiobarbituric acid-reactive material (as an indicator of lipid peroxidation) in the mitochondrial subfraction.

Result : The most dramatic changes observed were a 5-9-fold increase in mitochondrial protein, a 3-6-fold increase in the microsomal content of cytochrome P450, a 3-10-fold increase in cytosolic DT-diaphorase activity, an approximately 2-fold increase in cytosolic epoxide hydrolase activity and as much as a 60% decrease in the level of thiobarbituric acid-reactive compounds in the mitochondrial fraction. Smaller increases in microsomal epoxide hydrolase activity and decreases in cytosolic glutathione peroxidase activity were also observed. Of the perfluoro fatty acids tested, perfluorooctanoic acid caused the largest changes in the parameters examined here. Dietary exposure of mice to a 0.02% dose of this substance for 10 days results in a maximal or near-maximal effect in most cases.

Test substance : PFOA

05.12.2005 (498)

Type : Sub-chronic

Species	:	mouse
Sex	:	male
Strain	:	C57BL
Route of admin.	:	oral feed
Exposure period	:	10 days
Frequency of treatm. Post	:	Daily
exposure period	:	
Doses	:	0.02 and 0.1%
Control group	:	
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	other TS

Method : The relationship of dose and time related factors as well as chain lengths to the effects of perfluoro fatty acids on peroxisome proliferation and mitochondrial size in mouse liver was investigated. Male C57B1/6-mice were administered perfluoro fatty acids in the diet, and at the end of the treatment periods, subcellular fractions of the liver were prepared and analyzed.

Result : Results showed that PFOA in the diet at doses of 0.02 or 0.1% weight per weight (w/w) caused decreases in body weight and increases in liver weight. It also caused a dramatic increase in the protein content of the mitochondrial fraction (8- to 9-fold with 2% PFOA, and 4-fold with 1% PFOA). Peroxisomal palmitoyl- coenzyme-A beta-oxidation, lauroyl-coenzyme-A-oxidase, and catalase activities were significantly increased after PFOA treatment, the largest effects being observed after exposure to 0.02% PFOA for 10 days. Dietary exposure to as little as 0.001% PFOA brought about significant increases in these parameters. To determine the effect of chain length, animals were fed 0.02% w/w perfluoroacetic-acid (PFAA), perfluorobutyric-acid, PFOA, and perfluorodecanoic acid (PFDA) for 10 consecutive days. No significant effects were seen with PFAA, and the greatest increase of liver weight was with PFOA, while the greatest decrease in body weight was with PFDA. Increases in the protein content of the hepatic mitochondrial fractions resulted with all the tested perfluoro fatty acids, and PFOA and PFDA were the most effective. PFOA and PFDA significantly increased peroxisomal fatty acid beta-oxidation, but all of them decreased catalase activity. The authors conclude that perfluoro fatty acids increase mitochondrial protein primarily due to a redistribution of mitochondria from the nuclear fraction to the mitochondrial fraction due to a post treatment decrease in size.

Test substance : PFOA

05.12.2005 (499)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	no data
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	6 days
Frequency of treatm. Post	:	Daily
exposure period	:	
Doses	:	
Control group	:	yes
Method	:	other
Year	:	1998
GLP	:	no data
Test substance	:	other TS

Method : Niemann-Pick type C disease is an inherited disorder characterized by lysosomal accumulation of cholesterol and the mutant gene has recently been identified. The predicted gene product is a transmembrane protein

showing homology to proteins involved in the regulation of cholesterol homeostasis, such as 3-hydroxy-3-methylglutaryl-coenzyme A and the sterol regulatory element binding protein cleavage-activating protein. Recent investigations have established a peroxisomal deficiency, which raised the question of whether peroxisomal proliferation could affect this cholesterol-processing error.

Result : Mutant mice with Niemann-Pick type C disease were treated with the peroxisomal inducer perfluorooctanoic acid (0.05% in the diet for 6 days), which increased peroxisomal beta-oxidation and catalase activity to the same level as in control mice. Not only the peroxisomal, but also the lysosomal malfunctions were corrected and the cholesterol content was decreased. Clofibrate (0.6% in the diet for 3 weeks), another peroxisomal inducer, restored both peroxisomal enzyme activities and ubiquinone content. It appears that in Niemann-Pick type C disease treatment with appropriate peroxisomal inducers restores basic cellular functions, indicating a relationship between peroxisomes and cholesterol homeostasis, and thereby may effectively interfere with the development of the disease.

Test substance : PFOA

05.12.2005 (541)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : C57BL
Route of admin. : oral feed
Exposure period : 5 days
Frequency of treatm. Post : Daily
exposure period : 20 days
Doses : 0.05%
Control group :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : Male C57Bl/6 mice were treated for 5 days with 0.05% PFOA in their diet to determine the effect of PFOA on induction of peroxisomal fatty acid beta-oxidation in the liver. Recovery was investigated during a 20-day recovery period.

Result : This treatment resulted in a potent induction of peroxisomal fatty acid beta-oxidation in the liver. In order to investigate recovery from treatment with PFOA, mice were given normal laboratory chow for up to 20 days after termination of PFOA administration. It was established that the activities of peroxisomal lauoryl-CoA oxidase and palmitoyl-CoA oxidation were still elevated 2-3 weeks after termination of treatment. The catalase activity recovered in the cytosolic fraction was also still significantly elevated after 20 days with normal laboratory chow. Furthermore, the protein content of the mitochondrial fraction was increased by PFOA and had not returned to control level at the end of the recovery period. PFOA also caused a persistent effect in omega hydroxylation of lauric acid (cytochrome P-452). The activities of cytosolic DT-diaphorase and glutathione transferase were also enhanced by PFOA. However, these two enzymes recovered relatively rapidly from the treatment (2-20 days). This study reveals two different patterns of recovery from PFOA treatment, one involving parameters that recovered completely, or almost completely, from PFOA treatment after 20 days and another involving parameters that were still elevated at the end of the recovery period.

Test substance : PFOA

05.12.2005 (571)

Type : Sub-chronic

Species	:	mouse
Sex	:	male/female
Strain	:	C57BL
Route of admin.	:	oral feed
Exposure period	:	5 to 10 days
Frequency of treatm. Post	:	Daily
exposure period	:	
Doses	:	0.02 to 0.05%
Control group	:	
Method	:	other
Year	:	1992
GLP	:	no data
Test substance	:	other TS

Method : Male and female C57Bl/6 mice were administered PFOA (0.02-0.05% w/w for 5-10 days) in their diet to determine the effect of PFOA on induction of peroxisomal fatty acid beta-oxidation in the liver.

Result : This treatment resulted in a several-fold induction of hepatic peroxisomal fatty acid beta-oxidation (monitored as increases in cyanide-insensitive palmitoyl-CoA oxidation, lauroyl-CoA oxidase and catalase activity) in all animals. The protein content of the hepatic mitochondrial fraction was also increased in all mice exposed to PFOA. Furthermore, studies on xenobiotic-metabolizing enzymes revealed no sex-related difference in the response to PFOA. All mice demonstrated a dramatic increase in omega-hydroxylation of lauric acid. Cytosolic epoxide hydrolase, glutathione transferase and DT-diaphorase activities were increased about 2-5-fold. These results with mice differ dramatically from previous studies and our own experiments here with Wistar rats, in which exposure to PFOA causes hepatic peroxisome proliferation in male animals, whereas females are unaffected.

Test substance : PFOA

05.12.2005 (569)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male
Strain	:	C57BL
Route of admin.	:	oral feed
Exposure period	:	
Frequency of treatm. Post	:	
exposure period	:	
Doses	:	0.05%
Control group	:	
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	other TS

Method : Male C57B1/6-mice were administered 0.05% in the diet of PFOA, PFOSA, or octanesulfonic acid (OSA) to determine the effect of PFOA on induction of peroxisomal fatty acid beta-oxidation in the liver. The action of perfluorooctanesulfonic acid (PFOSA) in peroxisomal fatty acid oxidation and other activities in the mouse liver known to be affected by peroxisome proliferators was also investigated. At the end of treatment, mice were killed and livers were removed, homogenized, and subjected to differential centrifugation. Fractions were assayed for peroxisomal fatty acid beta-oxidation, omega-hydroxylation of lauric-acid, and activities of peroxisomal catalase, cytosolic epoxide-hydrolase, and cytosolic DT-diaphorase.

Result : Results showed that PFOSA was almost as potent as PFOA in inducing increases of all these parameters. OSA was ineffective at doses used for PFSOA and PFOA. The finding that OSA, which is more easily metabolized than PFOSA is much less potent as a peroxisome proliferator seemed

compatible with the hypothesis that formation of a xenobiotic acyl-coenzyme-A was the first step in peroxisome proliferation. The authors conclude that the fact that all the parameters normally affected by peroxisome proliferators are affected by PFOSA supports the coregulation of these parameters and peroxisome proliferation. They add that the latter effect of PFSOA challenges the hypothesis that the mechanism underlying the effects of peroxisome proliferators is the formation of a thioester between the coenzyme-A and the carboxylic group of the proliferator.

Test substance : PFOA

05.12.2005 (567)

Type : Sub-chronic
Species : mouse
Sex : male
Strain :
Route of admin. : oral feed
Exposure period : 10 days
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.02%
Control group :
Method : other
Year : 1995
GLP : no data
Test substance : other TS

Method : Vitamin A-deficient male mice were treated for 10 days with 0.02% PFOA in their diet to determine the effect of PFOA on induction of peroxisomal fatty acid beta-oxidation in the liver. The effects of this highly potent peroxisome proliferator on peroxisomal palmitoyl-CoA oxidation and lauroyl-CoA oxidase activities were determined.

Result : The effects of PFOA on peroxisomal palmitoyl-CoA oxidation and lauroyl-CoA oxidase activities were reduced by 3.1-7.5 times in comparison to the values obtained with mice receiving a vitamin A-adequate diet. The activity of peroxisomal catalase was virtually unaffected by vitamin A deficiency and treatment with PFOA had no significant effect on this activity in vitamin A-adequate or vitamin A-deficient mice. However, vitamin A deficiency itself caused a more than 800% increase in cytosolic catalase activity. Thus, the percentage increase caused by PFOA on cytosolic catalase activity was reduced 12.6 times in vitamin A-deficient mice compared to the increase in vitamin A-adequate mice, although the total absolute activities were similar. These findings suggest that the peroxisome proliferation caused by this peroxisome proliferator is highly dependent on the vitamin A status of the mouse.

Test substance : PFOA

05.12.2005 (570)

Type : Sub-chronic
Species : mouse
Sex : no data
Strain : C57BL
Route of admin. : oral feed
Exposure period : 10 days
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.02%
Control group :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : Vitamin A-adequate and vitamin A-deficient C57B1/6 mice were treated for ten days with 0.02% (w/w) PFOA in their diet to determine the effect of PFOA on induction of peroxisomal fatty acid beta-oxidation in the liver. The effects of this highly potent peroxisome proliferator on peroxisomal palmitoyl-CoA oxidation and lauroyl-CoA oxidase activities were determined.

Result : Treated vitamin A adequate and deficient mice demonstrated approximately the same increases in liver somatic index (g liver/g body weight) (somewhat more than 2-fold) and mitochondrial protein content (5-fold). PFOA treatment resulted in a 26-fold increase in hepatic peroxisomal lauroyl-CoA oxidase activity in vitamin A-adequate mice, whereas the same activity was unchanged in vitamin A-deficient mice. Vitamin deficiency itself caused a 3- to 4-fold increase in cytosolic catalase activity and a smaller increase in the activity of microsomal cytochrome P-450 IVA (lauric acid omega- and omega-1 hydroxylase) in this same organ. The induction of the activities of these enzymes was less prominent in vitamin A-deficient mice compared with the effect caused by PFOA in vitamin A-adequate mice, resulting in approximately the same maximal values for these parameters in both groups (i.e. approximately 21 micromol/g liver-min and 350 nanomol/g liver-min, respectively). A 70 kDa protein, presumable the multifunction protein, was shown by Commassie blue staining of SDS-polyacrylamide gels and by immunoblotting (with antibodies towards the multifunctional protein) to be induced to approximately the same degree in vitamin A-adequate and deficient mice. A morphometric study revealed that PFOA causes the same extent of hepatic peroxisome proliferation in vitamin A-deficient as in vitamin A-adequate mice. The possibility that PFOA exerts its effect in vivo through at least two different mechanisms is discussed.

Test substance : PFOA

05.12.2005 (572)

Type : Sub-chronic
Species : mouse
Sex :
Strain :
Route of admin. : oral feed
Exposure period : 7 days
Frequency of treatm. Post : Daily
exposure period : 10 days
Doses :
Control group :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : It has previously been demonstrated that severe adipose tissue atrophy occurs upon dietary treatment of mice with potent peroxisome proliferators (PPs). This atrophy occurs subsequent to peroxisome proliferation in the liver and may represent a novel addition to the pleiotropic effects exerted by PPs. In the present study, the recovery of mice from such atrophy following cessation of exposure was characterized.

Result : Following termination of treatment with PFOA for 7 days, the adipose tissue atrophy was rapidly reversed, beginning on 2-5 days of recovery and being complete within 10 days. In contrast, hepatic peroxisome proliferation recovered much more slowly, indicating that these processes are not strictly coordinated. Analysis of lipoprotein lipase and hormone-sensitive lipase activities in adipose tissue revealed that the decrease and increase in these activities, respectively, caused by PFOA were both reversed within 10 days of recovery. Overall, these data provide further support for the previous conclusion that the adipose tissue atrophy induced by PFOA is caused, at least in part, by changes in the activities of lipoprotein lipase

and hormone-sensitive lipase. The serum level of cholesterol, which increased after termination of PFOA treatment, returned to normal with a time-course similar to the recovery of adipose tissue weight, although hepatic peroxisome proliferation was still present.

Test substance : PFOA

05.12.2005 (636)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : other: ddY
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.025, 0.05, 0.1, and 0.2% (w/w)
Control group : yes
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : The effects were studied of dietary administration of 1H,1H,2H,2H-perfluorodecanol (8-2 telomer alcohol) on peroxisome proliferation in the liver of mice. Male ddY mice were fed on a diet containing 8-2 telomer alcohol at concentrations of 0, 0.025, 0.05, 0.1, and 0.2% (w/w) for 7, 14, 21, and 28 days.

Result : These treatments with 8-2 telomer alcohol caused liver enlargement in a dose- and duration-dependent manner. Peroxisome proliferation in the liver of mice was confirmed by electron microscopic examination. Peroxisomal acyl-CoA oxidase was induced by these treatments with 8-2 telomer alcohol in a dose- and time-dependent manner. The concentration of PFOA and related compounds were determined in the liver and plasma, since PFOA had been shown to be a possible metabolite of 8-2 telomer alcohol and to cause significant peroxisome proliferation in rodents. Five metabolites, namely, PFOA, perfluorononanoic acid (PFNA), 2H,2H-perfluorodecanoic acid (8-2 telomer acid), and two unidentified metabolites, were present in the liver and serum. PFOA was confirmed to be accumulated in the liver of mice following the administration of 8-2 telomer alcohol in a dose- and duration-dependent manner. A linear relationship was observed between the concentration of PFOA and the activity of peroxisomal acyl-CoA oxidase in the liver of mice. These results strongly suggest that PFOA, but not 8-2 telomer alcohol itself, caused peroxisome proliferation in the liver. The present study provided evidence that 8-2 telomer alcohol is converted into PFOA in vivo and that the PFOA formed produces biological effects in the liver of mice.

Test substance : 8-2 Telomer alcohol (1H,1H,2H,2H-perfluoro-1-decanol)

05.12.2005 (394)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : other: Crl:CD-1(ICR)BR
Route of admin. : gavage
Exposure period : 14 days
Frequency of treatm. Post : Daily
exposure period : None
Doses : 0.3, 1, 3, 10, or 30 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 2004
GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : Ammonium perfluorooctanoate (APFO), as formerly used in the production of commercial products, was a mixture of linear and branched isomers in a ratio of approximately 80:20 (linear/branched). The extensive toxicologic database for APFO has been developed essentially using this mixture of isomers. The current production of APFO uses a synthetic process that produces only the linear isomer. The present study was undertaken to compare the biologic activity of linear/branched APFO with that of linear APFO. In addition, a form of APFO consisting of only branched molecules was also evaluated.

Rats and mice were given doses by oral gavage ranging from 0.3 to 30 mg/kg of either the linear/branched, linear, or branched APFO for 14 days. Clinical signs, body weights, food consumption, selected hematology and serum lipid parameters, liver and kidney weights, hepatic peroxisomal beta-oxidation, and serum PFOA concentrations were evaluated for each of the three test materials in each of the two rodent species.

Result : Clinical signs were generally unremarkable in rats and mice dosed with linear/branched, linear, or branched APFO. Mean body weights were 19, 19, and 5% lower than that of controls in rats dosed with 30 mg/kg of linear/branched, linear, and branched APFO, respectively. Similar changes were present in mice (means were 21, 18, and 3% lower than that of controls, respectively). Ex vivo hemolysis was seen in rats but not mice. In rats, total cholesterol, HDL, and non-HDL cholesterol decreases were produced by all 3 materials. Triglycerides were decreased to a similar extent with the linear form producing a response at a lower dose. In mice, all 3 forms reduced both total and HDL cholesterol similarly but, unlike in the rat, triglycerides were increased at low doses, but similar to control or decreased at the highest dose. Liver weight increases were seen in both species with all three forms. Increased hepatic beta-oxidation activity was seen in both species but was least pronounced in rats given the branched material. In mice, all doses produced increased hepatic beta-oxidation activity with little difference noted either by material form tested or dose. In rats, serum PFOA levels were approximately 50 ppm at the LOEL of 1 mg/kg for linear/branched and branched material, and 20 ppm at the LOEL of 0.3 mg/kg for the linear material (LOELs based primarily upon lipid parameters). In mice, serum PFOA levels were similar for all 3 materials. At the LOEL (0.3 mg/kg, based upon liver weight), serum PFOA levels were 10-14 ppm. In both rats and mice, the overall responses to the linear/branched and the linear forms of PFOA were similar, but the branched form appears to be less potent. Based on these results, the toxicological database developed primarily from testing linear/branched APFO is applicable to linear APFO.

05.12.2005 (228)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : gavage
Exposure period : 3 weeks
Frequency of treatm. Post : 3 doses per week (total of 9 doses)
exposure period : 3 days
Doses : 0.1, 1.0, or 10 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 5 male and 5 female Crl:CD rats and 5 male and 5 female CD-1

mice mice were administered the test substance, as an aqueous solution, by intragastric intubation. Control rats and mice received water only. Body weights and clinical signs were recorded. Animals were sacrificed 3 days after the final dose and the livers were removed and weighed.

Result : APFO was administered three times a week for three weeks to rats and mice at three dose levels, 0.1, 1.0 or 10 mg/kg. Weakness followed by death occurred in two female mice dosed at 10 mg/kg. Sporadic weight loss was seen in the female rats and both sexes of mice. A significant liver weight increase was noted in both male and female mice administered 1 and 10 mg/kg. Significantly increased liver weights were also noted in male rats administered 10 mg/kg.

05.12.2005 (192)

Type : Sub-chronic
Species : mouse
Sex : no data
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1997
GLP : no data
Test substance : other TS

Method : The effects of PFOA on the levels of lipids in liver and serum were compared between mice fed a diet supplemented with soy bean oil (SO), perilla oil (PO), or fish oil (FO) for 4 weeks.

Result : Hepatic content of triglyceride (TG) was significantly lower in the mice fed the FO diet than that in the mice fed either the SO or the PO diet. The treatment with PFOA caused a marked accumulation of TG in the livers of SO-fed and PO-fed mice (seven- and twofold over their respective controls), whereas a level of TG remained low in the mice fed the FO diet. Incorporation in vivo of [3H]glycerol revealed that FO-feeding reduced synthesis of TG in the liver. The administration of PFOA increased the incorporation of [3H]glycerol into hepatic phospholipid (PL) regardless of the dietary oil, while synthesis of hepatic TG from [3H]glycerol was not altered by the treatment with PFOA. Serum level of TG was reduced by the administration of PFOA to the mice fed either the SO diet or the PO diet, while no change in the level was observed in the mice fed the FO diet. These results suggest that the accumulation of TG in the livers of PFOA-treated mice is due to the inhibition of the secretion of TG into circulation. PFOA-induced hepatic accumulation of TG is prevented by the feeding of the FO diet which inhibits TG formation. Among three dietary oils, FO-feeding alone prevented the PFOA-caused accumulation of TG in the liver. The importance of docosahexaenoic acid (22:6(n - 3)) is discussed in relation to the prevention of fatty liver induced by chemicals.

Test substance : PFOA

05.12.2005 (389)

Type : Sub-chronic
Species : mouse
Sex : no data
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :

Control group :
Method : other
Year : 2001
GLP : no data
Test substance : other TS

Method : The effects of PFOA on the synthesis of phospholipids were studied in combination with feeding of various dietary oils (soybean oil (SO), perilla oil (PO) or fish oil (FO)) to mice.
Result : Hepatic contents of phosphatidylcholine (PtdCho), phosphatidylethanolamine (PtdEtn) and phosphatidylinositol (PtdIns) did not differ between the three dietary groups except for a high level of PtdEtn in FO-fed mice. PFOA treatment increased the hepatic content of PtdCho and PtdEtn by 1.5 fold but did not affect that of PtdIns. Fatty acid compounds of phospholipids were different between the three groups reflecting the fatty acid composition in their diet. The rate of incorporation of [3H]glycerol into PtdEtn in the FO-fed group was significantly higher and that into TG was lower, compared to other dietary groups in PFOA-untreated mice. PFOA treatment significantly increased the incorporation of [3H]glycerol into PtdEtn and PtdSer and decreased that into TG, whereas those into other lipid classes were not altered by PFOA treatment. These results suggest that acceleration of PtdEtn synthesis de novo is responsible for a marked increase in the hepatic content of PtdEtn in PFOA-treated mice, whereas an increase in hepatic content of PtdCho is thought not to be due to increased synthesis de novo.
Test substance : PFOA
05.12.2005 (390)

Type : Sub-chronic
Species : mouse
Sex :
Strain :
Route of admin. : oral unspecified
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : The effects of peroxisome proliferators (PP) on adipose tissue in mice were characterized.
Result : Treatment with potent PP, such as PFOA, 2-methyl-2-(p-(1,2,3,4-tetrahydroxynaphthyl)phenoxy)propionic acid, (4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio)acetic acid, and di(2-ethylhexyl)phthalate, caused dramatic decreases in adipose tissue weight, whereas the moderately potent PP, acetylsalicylic acid, had a relatively weak effect. This decrease in weight reflects a loss of fat from adipocytes rather than a loss of cells, as demonstrated by constant DNA content. The dose-dependency and time-course experiments. indicate that peroxisome proliferation occurs simultaneously with or prior to adipose tissue atrophy. Thus, hepatic peroxisome proliferation might result in the increased mobilization of lipids and lipid utilization in liver. The enhanced adipose tissue hormone-sensitive lipase (HSL) activity and down-regulated lipoprotein lipase (LPL) activity observed upon PP treatment might, at least in part, explain the loss of fat via increased FA release from adipocytes and/or decreased FA uptake from the circulation, respectively In addition, the possible involvement of the increased tumor necrosis factor expression found upon PFOA treatment in reducing the insulin sensitivity of adipose tissue and

thereby altering LPL and HSL activities is discussed.

Test substance : PFOA

05.12.2005 (635)

Type : Sub-chronic
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 2 weeks
Frequency of treatm. Post : 6 hours a day, 5 days a week
exposure period : 14 days
Doses : 100 mg/kg
Control group : no
Method :
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : A group of 10 male and 10 female adult albino rabbits of the New Zealand breed was administered a dermal dose level of 100 mg/kg of body weight, 6 hours a day, 5 days a week, for 2 weeks. The test material was applied to the intact skin on each animal's back. The area of application was covered with impervious plastic sheeting to provide an occlusive dressing. Collars were used to restrain the test animals during the exposure period. At the end of each exposure period, the collars and bandages were removed and the test material removed.

Initial, 7, 14, and 28-day body weights were determined as were any clinical signs noted during the 28-day observation period. Blood samples were collected prior to the initial application and again on days 7, 14, and 28 after initiation of the study. An interim sacrifice of 4 male and 4 female animals was conducted on day 14 with the remaining animals continuing for observation through the end of the 28-day study. A gross necropsy was conducted on all animals which died during the conduct of the study as well as all animals which were sacrificed on day 28.

Remark : A range-finding study was conducted to set the dose level for the main study. Groups of 2 male and 2 female rabbits were administered 100, 1000, or 2000 mg/kg of APFO and the skin area occluded. All of the rabbits administered 2000 mg/kg were dead within 8 days. For the 1000 mg/kg group, 3 of the 4 rabbits were dead within 9 days. No deaths occurred in the 100 mg/kg group.

Result : There were no deaths. Generally, the rabbits lost weight during the dosing period, but gained weight in the 2-week post-exposure observation period. Pharmacotoxic signs were not evident. At the 14 and 28 day sacrifices, no visible signs were noted. Blood fluorine levels were as follows: for males, 5.4, 6.8, and 4.6 ppm at days 7, 14, and 28, respectively, of the study; for females, blood fluorine levels were 10.1, 12.1, and 3.5 ppm, respectively.

Test condition : The test group was comprised of 10 male and 10 female rabbits.

The test material was wiped off after the 6-hour test period.

An interim sacrifice was performed on day 14 on 4 male and 4 female rabbits; necropsies were conducted on the rest of the rabbits at day 28.

05.12.2005 (521)

Type : Sub-chronic
Species : monkey
Sex : male/female
Strain : other: Rhesus monkey
Route of admin. : gavage
Exposure period : 90 days

Frequency of treatm.	:	Daily
Post exposure period	:	None
Doses	:	3, 10, 30, or 100 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1978
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Ten male and 10 female rhesus monkeys were assigned to 5 groups, 2 per sex per group for a 90-day study. The test material was suspended in 0.5% Methocel and administered by stomach tube at dose levels of 0, 3, 10, 30, or 100 mg/kg/day. The animals were observed daily for general appearance and signs of toxicity; physical examinations were conducted monthly. Blood and urine samples were collected once in the pre-test and at one and 3 months of treatment following overnight fasting.

Hematology included hemoglobin, hematocrit, total erythrocytes, reticulocytes, total and differential leucocyte count, prothrombin time, activated partial thromboplastin time, and platelet count. Biochemical evaluations were for fasting blood glucose, blood urea nitrogen, serum glutamic pyruvic and glutamic oxalacetic transaminases, serum alkaline phosphatase, gamma-glutamyl peptidase, creatinine phosphokinase, cholesterol, total protein, albumin, sodium, potassium, chloride, and inorganic phosphate.

Urinalysis included color and appearance, volume, pH, specific gravity, qualitative tests for protein, glucose, ketone, bilirubin, occult blood, and microscopic examination.

All animals were examined for gross pathologic changes at necropsy. The heart, liver, adrenals spleen, pituitary, kidneys, testes/ovaries, brain, thyroid, and parathyroid were weighed and preserved for histopathologic examination.

Result : The monkeys treated with the higher dose, (100 mg/kg/day) all died during weeks two through five of the study. At the 30 mg/kg/day dosage level, three monkeys died during weeks 7-12. They all showed signs of toxicity in the gastrointestinal tract (anorexia, emesis, sometimes brown in color, black stools), pale face and gums, swollen face and eyes, slight to severe decreased activity and prostration. The monkeys of the 30 and 100 mg/kg/day dosage levels showed body weight losses from the first week of the study. Because of the early deaths of the monkeys at the 100 mg/kg/day dosage level, the clinical laboratory tests were not conducted. Mean serum PFOA was 50 ppm in males and 58 ppm in females in the 3 mg/kg/day group. At the same dose, males had 3 ppm and females 7 ppm in liver samples. At 10 mg/kg/day, males had a mean serum PFOA of 58 ppm and females 75 ppm. Liver levels were 9 and 10 ppm for males and females, respectively, measured as organic fluoride. The monkeys at the 30 mg/kg/day dosage level showed, in the first month of the study, slight increase in prothrombin time and in activated partial thromboplastin time (A.P.T.T.) values, as well as decreased alkaline phosphatase activity in the serum (statistically significant). Only one monkey from this dosage level in this period showed a low albumin value. At the end of the study, the only remaining monkey from the 30 mg/kg/day dosage level showed apparent anemia, low blood glucose, alkaline phosphatase, total protein and albumin values. There was no mortality at the 10 mg/kg/day dosage level. One monkey had black stool on several days in week 12 and occasionally anorexia and one monkey exhibited pale face and gums. At this dosage level there was a very slight increase in the A.P.T.T. values in the female monkeys during the first month of the study (not statistically significant). There were no changes in the other indices and no changes in the body weight. In single monkeys from the 3 and 10 mg/kg/day dosage levels,

there were trends toward decreased alkaline phosphatase in the serum. In the control and the 3 mg/kg/day dosage level there was no mortality, no changes in the body weights and no signs of toxicity. Soft stool, diarrhea or emesis were observed occasionally. The mortality and the above mentioned signs of toxicity in the 30 and 100 mg/kg/day dosage levels were compound-related. There was a trend toward the same signs of toxicity in single monkeys at the 10 mg/kg/day dosage level. The 3 mg/kg/day dosage level seems to be free of signs of toxicity. There is an evident relationship between the administered doses and the degree of the toxicity.

No gross or microscopic lesions which were considered compound-related were seen in tissues other than the adrenals, bone marrow, spleen and lymph nodes for male and female monkeys at the 30 and 100 mg/kg/day dosage levels. Microscopically, the adrenals from male and female monkeys at the 30 and 100 mg/kg/day dosage levels have compound-related marked diffuse lipid depletion; the bone marrow from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound-related slight to moderate hypocellularity; the spleen and lymph nodes from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound related moderate atrophy of lymphoid follicles. Statistically significant variations in sex group mean weights of a few organs occurred between the control and experimental groups. These variations were of unknown biological significance and were not accompanied by morphological alterations.

Test condition : There were 2 male and 2 female monkeys in the test and control groups.

The vehicle was 0.5% Methocel.

05.12.2005 (285) (339)

Type : Sub-chronic
Species : monkey
Sex : male
Strain :
Route of admin. : other: Capsule
Exposure period : 4 weeks
Frequency of treatm. Post : Daily
exposure period : None
Doses : 2 or 20 mg/kg
Control group : yes
Method : other
Year : 2001
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Male cynomolgus monkeys were administered an oral capsule containing 0, 2, or 20 mg/kg/day APFO for 4 weeks. There were 3 monkeys in the 2 and 20 mg/kg/day groups and one monkey in the control group. The monkeys weighed 2.1 to 3.6 kg at the start of treatment.

Animals were observed twice daily for mortality and moribundity and were examined at least once daily for signs of poor health or abnormal behavior. Food consumption was assessed qualitatively. Body weight data were recorded before the start of treatment, on day 1 of treatment and weekly thereafter.

The monkeys were fasted overnight and blood samples were collected one week prior to the start of the study and on day 30 for clinical hematology and clinical chemistry analyses, and hormone and PFOA level. Blood for clinical chemistry was also collected from each animal on day 2 (approximately 24 hours after the first dose). Samples were analyzed for estradiol, estrone, estriol, thyroid stimulating hormone, total and free

triiodothyronine, and total and free thyroxin.

At scheduled necropsy, samples of the right lateral lobe of the liver were collected from each animal and analyzed for palmitoyl CoA oxidase activity. Representative samples of liver, right and left testes, and pancreas were collected from each animal for cell proliferation evaluation using proliferation cell nuclear antigen. Bile was collected from each animal for bile acid determination. A sample of liver was collected from each animal for PFOA concentration.

The following tissues (when present) or representative samples were collected and preserved in 10 % neutral-buffered formalin, unless otherwise specified, for possible future examination: adrenal (2), aorta, brain, cecum, colon, duodenum, epididymis (2), esophagus, eyes [preserved in Davidson's fixative (2)], femur with one marrow (articular surface of the distal end), gallbladder, heart, ileum, jejunum, kidney (2), lesions, liver, lung, lymph node (mesenteric) mammary gland, muscle (thigh), pancreas, pituitary, prostate, rectum, salivary gland [mandibular (2)], sciatic nerve, seminal vesicle (2) skin, spinal cord (cervical, thoracic, and lumbar), spleen, sternum with bone marrow, stomach, testis (2), thymus, thyroid (2) with parathyroid, trachea, and urinary bladder. The adrenals, liver, pancreas, spleen, and testes from each animal were embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined microscopically.

Result : All animals survived to scheduled sacrifice. There were no clinical signs of toxicity in the treated groups and there was no effect on body weight. Low or no food consumption was observed for one animal given 20 mg/kg/day. No food consumption was noted for this animal on day 12 and low food consumption was noted on days 5, 7, 11, 14 17, and 24, respectively. For this animal, decreased food consumption is in all likelihood related to APFO administration. There were no effects on estradiol, estriol, thyroid stimulating hormone, total and free triiodothyronine, and total and free thyroxin. Estrone levels were notably lower for males given 2 and 20 mg/kg/day APFO. There was no evidence of peroxisome proliferation or cell proliferation in the liver, testes or pancreas of treated monkeys. No adverse effects were noted in either gross or clinical pathology studies.

05.12.2005 (140)

Type : Sub-chronic
Species : monkey
Sex : male
Strain : other: Cynomolgus
Route of admin. : other: Capsule
Exposure period : 26 weeks
Frequency of treatm. Post : Daily
exposure period : 13 weeks
Doses : 3, 10, or 30 mg/kg (the 30 mg/kg dose was reduced to 20 mg/kg on day 20 of the study)
Control group : yes, concurrent no treatment
Method : other
Year : 2001
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO is a processing aid in the production of fluoropolymers that has been shown to have a long half-life in human blood. To understand the potential toxicological response of primates, groups of male cynomolgus monkeys were given daily po (capsule) doses of either 3, 10, or 30 (reduced to 20) mg/kg/day for 26 weeks. Two monkeys from each of the control and 10 mg/kg/day dose groups were observed for 90 days after the last dose. Clinical observations, clinical chemistry, determination of key hormones, gross and microscopic pathology, cell proliferation, peroxisomal

proliferation, bile-acid determination, and serum and liver perfluorooctanoate PFOA concentrations were monitored.

Result : Toxicity, including weight loss and reduced food consumption, was noted early in the study at the 30 mg/kg/day dose; therefore, the dose was reduced to 20 mg/kg/day. The same signs of toxicity developed in 3 monkeys at 20 mg/kg/day, after which treatment of these monkeys was discontinued. One 30/20 mg/kg/day monkey developed the signs of toxicity noted above and a possible dosing injury, and this monkey was sacrificed in extremis on Day 29. A 3 mg/kg/day dose-group monkey was sacrificed in extremis on Day 137 for reasons not clearly related or unrelated to APFO treatment. Dose-dependent increases in liver weight as a result of mitochondrial proliferation occurred in all APFO-treated groups.

Histopathologic evidence of liver injury was not observed at either 3 or 10 mg/kg/day. Evidence of liver damage was seen in the monkey sacrificed in moribund condition at the highest dose. Body weights were decreased at 30/20 mg/kg. PFOA concentrations in serum and liver were highly variable, were not linearly proportional to dose, and returned to background levels within 90 days after the last dose. A no observable effect level was not established in this study, and the low dose of 3 mg/kg/day was considered the lowest observable effect level based on increased liver weight (and uncertainty as to the etiology leading to the moribund sacrifice of one low-dose monkey on Day 137). Other than those noted above, there were no APFO-related macroscopic or microscopic changes, changes in clinical chemistry, hormones, or urinalysis, or hematological effects. In particular, effects that have been associated with the development of pancreatic and testicular toxicity in rats were not observed in this study. Serum cholecystokinin (CCK) concentrations were not altered in these monkeys.

Test condition : The control group was administered empty gelatin capsules.

One monkey in the low-dose group had to be replaced for non-treatment related issues. The replacement monkey received his initial dose on day 17.

Dosing for the high-dose was discontinued from day 12 through 21 because of toxicity. Dosing was recommenced at 20 mg/kg on day 22. Also due to toxicity, dose administration was discontinued for 3 of the 6 monkeys on day 43, 66, and 81.

Two monkeys in each of the control and mid-dose groups were designated as recovery group monkeys and observed for 13 weeks after the 26-week treatment period.

05.12.2005 (107) (210) (413) (601)

Type : Sub-chronic
Species :
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatm. Post :
exposure period :
Doses :
Control group :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : This study was undertaken to investigate the role of adrenal hormones in hepatomegaly and peroxisomal enzyme induction caused by peroxisomal proliferators and to further delineate the interrelationship between these

parameters.

Remark : Few details were available.

Result : Because adrenalectomy alters hepatic drug metabolism, this study used the non-metabolizable proliferator PFOA. Hepatomegaly caused by PFOA depends on corticosterone, the major glucocorticoid in rodents. Liver growth caused by PFOA appears to be predominantly hypertrophic in nature, and DNA synthesis in response to PFOA predominates in periportal regions of the liver lobule. Data also show that although induction of peroxisomal beta-oxidation by PFOA is independent of adrenal hormones, induction of catalase is dependent on the presence of these hormones. This study supports the contention that induction of activities of various peroxisomal enzymes is controlled by different regulatory mechanisms.

Test substance : PFOA

05.12.2005 (597)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing Test : Salmonella typhimurium TA-98, TA-100, TA-1535, TA-1537, and TA-1538
concentration : 0.1 ug to 500 ug per plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The Salmonella/Mammalian-Microsome Reverse Mutation Assay was used to evaluate the test article and/or its metabolites for their ability to induce reverse mutations at the histidine locus in the genome of specific Salmonella typhimurium tester strains both in the presence and absence of an exogenous metabolic activation system of mammalian microsomal enzymes derived from Aroclor-induced rat liver (S9).

APFO was treated over a series of concentrations such that there were either quantitative or qualitative evidence of some chemically-induced physiological effect at the highest dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was 0.1 to 500 ug per plate.

The tester strains used in the mutagenicity assay were Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, TA1538. The assay was conducted with 5 doses of test article in both the presence and absence of S9 mix along with concurrent vehicle and positive controls. The doses tested were 100, 333, 1000, 3330, and 5000 ug per plate in both the presence and absence of S9 mix.

Result : APFO was tested in microbial assays using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. All tests were negative with and without activation

Test condition : The test with TA-100 was repeated at 100, 500, and 1000 ug because of increased revertants observed at the 500 ug dose level in the initial test.

05.12.2005 (285) (417)

Type : Gene mutation in Saccharomyces cerevisiae
System of testing Test : Saccharomyces cerevisiae strain D-4
concentration : 0.1-500 ug per plate
Cycotoxic concentr. :
Metabolic activation : with and without

Result : negative
Method : other
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO was evaluated in an in vitro microbial assay employing the Saccharomyces cerevisiae indicator organism. APFO was tested directly and in the presence of an exogenous metabolic activation system of mammalian microsomal enzymes derived from Aroclor-induced rat liver (S9).

APFO was tested over a series of concentrations such that there were either quantitative or qualitative evidence of some chemically-induced physiological effect at the highest dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of APFO was 0.1 to 500 ug per plate.

The tester strain used in this assay was Saccharomyces cerevisiae D4. The assay was conducted with 5 doses of APFO in both the presence and absence of S9 mix along with concurrent vehicle and positive controls. The doses tested were 100, 333, 1000, 3330, and 5000 ug per plate in both the presence and absence of S9 mix.

Result : APFO was tested employing Saccharomyces cerevisiae strain D-4. All tests were negative with and without activation.

05.12.2005 (285) (417)

Type : other: Cytotoxicity and cell transformation
System of testing Test : C3H 10T-1/2
concentration : 0 to 200 ug/mL (cytotoxicity); 0.1 to 200 ug/mL (range-finding study); and 1.0, 10, 100 ug/mL (foci transformation)
Cycotoxic concentr. : 50 ug/mL
Metabolic activation : without
Result : negative
Method : other
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The experimental procedures employed are the test methods described by Reznikoff, C., Brankow, D., and Heidelberger, C. (1973). Quantitative and qualitative studies of chemical transformation of cloned C3H mouse embryo cells sensitive to post-confluence inhibition of cell division. Cancer Res., 33:3239-3249.

The cell line used in this assay is designated C3H/10T1/2 CL8 derived from C3H mouse embryos. This cell line is highly sensitive to post-confluence inhibition of cell division. For the transformation test (12 dishes per group), 1000 cells obtained from freshly confluent dishes are seeded per 60 mm Petri dish in 5 mL of medium. 24 hours after seeding, the test chemical is added to the medium. The duration of the exposure is 24 hours, after which time a medium change is made. Medium is changed twice weekly until the cells reach confluence, then once weekly. Control cultures are handled the same way except that only acetone is added. At 6 weeks, dishes for the transformation assay and the controls are washed with 0.9% NaCl solution, fixed with methanol, stained with Giemsa, and scored for transformed foci. The PE is defined as the number of colonies formed as a percentage of the number of cells seeded. The transformation frequency is calculated as the percentage of cells that give rise to types II and III transformed foci corrected for the PE.

Cytotoxicity tests are done for each assay.

Result : APFO was studied in C3H 10T-1/2 cells for morphologic evidence of transformation in vitro. At the dose levels employed (1.0, 10, and 100 ug/mL), no evidence of transformation was observed.

05.12.2005 (251)

Type : Chromosomal aberration test
System of testing Test : CHO cells
concentration : 12.5, 25, 50, 75, 150, and 200 ug/mL
Cycotoxic concentr. : 501 ug/mL (no activation); 1670 ug/mL (with activation)
Metabolic activation : with and without
Result : negative
Method : other
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this in vitro assay was to evaluate the ability of APFO to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, with and without metabolic activation.

Remark : A range-finding assay was conducted wherein concentrations of 0.167, 0.501, 1.67, 5.01, 16.7, 50.1, 167, 501, and 5010 ug/mL were tested. Complete cytotoxicity was observed in the cultures dosed with 501, 1670, and 5010 ug/mL in the non-activation assay and with 1670 and 5010 ug/mL in the assay with metabolic activation. Very few metaphases were available in the culture treated with 167 ug/mL and a severe cell cycle delay was observed.

Result : In a chromosome aberration assay in CHO cells, APFO was considered negative for inducing chromosomal aberrations in CHO cells either in the presence or absence of metabolic activation.

05.12.2005 (132)

Type : HGPRT assay
System of testing Test : CHO-K1 cell line
concentration : 1:128, 1:256, 1:512
Cycotoxic concentr. : 1:128
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : This assay evaluated the mutagenic potential of a test article via its ability to induce mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. This locus is responsible for production of HGPRT, an enzyme that is present in normal cells and allows cells to salvage hypoxanthine and guanine from the culture medium in order to synthesize DNA. In normal cells, when a toxic substance called 6-thioguanine is included in the growth medium, it is salvaged by the HGPRT enzyme along with hypoxanthine and guanine and incorporated into DNA, thereby causing cell death. Exponentially growing cells, sensitive to the toxic effect of 6-thioguanine, were exposed to various concentrations of the test material. If the test material is potentially mutagenic, normal cells (which can utilize hypoxanthine, guanine, and 6-thioguanine) mutate to become incapable of utilizing hypoxanthine, guanine, or 6-thioguanine from the culture medium. However, mutant cells retain their ability to grow as well as normal cells in culture medium because DNA synthesis is made possible by alternate synthetic pathways. Taken together, these findings indicate that the basis for HGPRT mutants is the lack of ability to utilize the toxic 6-thioguanine. Therefore, cells that grow to form colonies in the presence of 6-thioguanine are assumed to have undergone mutation either spontaneously or by exposure to the test material.

Result : APFO did not induce mutations at the HGPRT locus in CHO cells. The statistically significant increase in the number of mutant colonies in positive controls in both activated and non-activated assays verified the proper functioning of the test system. Based on the evaluation criteria of the protocol, APFO is considered non-mutagenic under the experimental conditions employed.

25.10.2005 (600)

Type : Ames test
System of testing Test : Salmonella typhimurium TA98, TA100, TA1535, and TA1537
concentration : 100, 333, 1000, 3330, and 5000 ug per plate
Cycotoxic concentr. : Not cytotoxic at 5000 ug per plate
Metabolic activation : with and without
Result : negative
Method : other: The method used is based on that described by Ames, B. N., McCann, J., and Yamasaki, E. (1975). Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res., 31:347-364.
Year : 1975
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay was used to evaluate APFO and/or its metabolites for their ability to induce reverse mutations at the histidine locus in the genome of specific Salmonella typhimurium tester strains and at the tryptophan locus in an Escherichia coli tester strain both in the presence and absence of an exogenous metabolic activation system of mammalian microsomal enzymes derived from Aroclor-induced rat liver (S9).

The doses tested in the mutagenicity assay were selected based on results of a dose range-finding study using tester strains TA100 and WP2uvrA and 10 doses of test article ranging from 6.67 to 5000 ug per plate, one plate per dose, both in the presence and absence of S9 mix.

The tester strains used in the mutagenicity assay were Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, and Escherichia coli tester strain WP2uvrA. The assay was conducted with 5 doses of test article in both the presence and absence of S9 mix along with concurrent vehicle and positive controls using 3 plates per dose. The doses tested were 100, 333, 1000, 3330, and 5000 ug per plate in both the presence and absence of S9 mix.

Result : APFO was tested twice for its ability to induce mutation in the Salmonella/mammalian-microsome reverse mutation assay. The tests were performed both with and without metabolic activation. A single positive response seen at one dose level in Salmonella typhimurium TA1537 when tested without metabolic activation was not reproducible. APFO did not induce mutation in S. typhimurium when tested either with or without mammalian activation.

05.12.2005 (129) (134)

Type : Escherichia coli reverse mutation assay
System of testing Test : Escherichia coli tester strain WP2uvrA
concentration : 100, 333, 1000, 3330, and 5000 ug/mL
Cycotoxic concentr. : No cytotoxicity at up to 5000 ug/mL
Metabolic activation : with and without
Result : negative
Method : other: The method used is based on that described by Green, M. H. L. and Muriel, W. J. (1976). Mutagen testing using trp+ reversion in Escherichia coli. Mutat. Res., 38:3-32.
Year : 1976
GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : The Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay was used to evaluate the test article and/or its metabolites for their ability to induce reverse mutations at the histidine locus in the genome of specific Salmonella typhimurium tester strains and at the tryptophan locus in an Escherichia coli tester strain both in the presence and absence of an exogenous metabolic activation system of mammalian microsomal enzymes derived from Aroclor-induced rat liver (S9).

The doses tested in the mutagenicity assay were selected based on results of a dose range-finding study using tester strains TA100 and WP2uvrA and 10 doses of APFO ranging from 6.67 to 5000 ug per plate, one plate per dose, both in the presence and absence of S9 mix.

The tester strains used in the mutagenicity assay were Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, TA1538, and Escherichia coli tester strain WP2uvrA. The assay was conducted with 5 doses of APFO in both the presence and absence of S9 mix along with concurrent vehicle and positive controls. The doses tested were 100, 333, 1000, 3330, and 5000 ug per plate in both the presence and absence of S9 mix.

Result : APFO was tested twice for its ability to induce mutation in the E. coli/mammalian-microsome reverse mutation assay. The tests were performed both with and without metabolic activation. APFO did not induce mutation in E. coli when tested either with or without mammalian activation.

05.12.2005 (129) (134)

Type : Chromosomal aberration test
System of testing Test : Human whole blood lymphocytes
concentration : 253, 505, 1010, and 1510 ug/mL (no activation); 505, 1010, 1510, and 2010 ug/mL (with activation)
Cycotoxic concentr. : 1670-5000 ug/mL (no activation); 5000 ug/mL (with activation)
Metabolic activation : with and without
Result : negative
Method : other
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : This assay is designed to establish whether the test article or its metabolites can interact with cells to induce chromosome breaks. Chemically induced lesions may result in breaks in chromatin that are either repaired by the cell in such a way as to be undetectable or result in visible damage. Aberrations are a consequence of failure or mistakes in repair processes such that breaks do not rejoin or rejoin in abnormal configurations. In order to detect chromosomal aberrations, cells must be in metaphase so that chromosomes are visible. The lymphocytes in blood do not usually divide and are stimulated to divide in culture by phytohemagglutinin. The cells are later arrested at the appropriate stage (metaphase) by Colcemid.

Result : APFO did not induce chromosomal aberrations in human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations.

Test condition : A dose-finding assay was conducted with and without metabolic activation. Concentrations ranged from 0.167 to 5000 ug/mL. Reductions of 57 and 100% were observed in the mitotic indices of the cultures dosed with 1670 and 5000 ug/mL without metabolic activation, respectively, as compared with the solvent control culture. Reduction of 100% was observed in the mitotic indices of the cultures dosed with 5000 ug/mL with metabolic activation, as compared with the solvent control culture.

In a confirmatory assay, replicate cultures were incubated with 125 to 2000 ug/mL in a 22.1 hour assay with 62.5 to 2000 ug/mL in a 46.0 hour assay under non-activation conditions. Replicate cultures were incubated with 250 to 3000 ug/mL in 22.1 and 46.0 hour assays with metabolic activation. No significant increase in cells with chromosomal aberrations, polyploidy, or endoreduplication was observed except for a weak increase in endoreduplication at 2000 ug/mL, an extremely toxic dose level, from the 46.0 hour activation assay.

25.10.2005 (130)

Type : Chromosomal aberration test
System of testing Test : Chinese hamster ovary (CHO) cells
concentration : 62.5 to 2000 ug/mL (no activation) and 250 to 4000 ug/mL (with activation)
Cycotoxic concentr. : Complete cytotoxicity at 5080 ug/mL with or without metabolic activation and 38-92% reduction in the mitotic index of the culture at 1690 ug/mL depending on the presence of metabolic activation.
Metabolic activation : with and without
Result : negative
Method : other
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this in vitro assay was to evaluate the ability of the test substance to induce chromosomal aberrations in CHO cells with and without metabolic activation.

Following a range-finding assay, replicate cultures of CHO cells were incubated with and without metabolic activation. Confirmatory trials were conducted with multiple harvests both in the presence and absence of metabolic activation.

Result : No significant increases in chromosomal aberrations were observed without activation. However, when tested with metabolic activation, APFO induced significant increases in chromosomal aberrations and in polyploidy at a single dose level that induced significant toxicity.

31.10.2005 (135)

Type : other: DNA-cell-binding assay
System of testing Test :
concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : positive
Method : other
Year : 1981
GLP : no data
Test substance : other TS

Method : This report describes a novel technique for screening potential carcinogens and mutagens. The DNA-cell-binding (DCB) assay is based on earlier observations which indicated that DNA and other nucleic acids exposed to active carcinogens strongly react with other macromolecules, producing nucleic acid--nucleic acid and nucleic acid--protein adducts. The latter group of adducts included complexes with proteins present in both prokaryotic and eukaryotic cell membranes. Increased attachment of DNA to the intact bacterial and animal cells was seen in the presence of active carcinogens or carcinogens activated by extracts from mouse and rat livers.
Result : PFOA was positive in the DNA-cell-binding assay.
Test substance : PFOA

19.10.2005 (387)

Type	:	Chromosomal aberration test
System of testing Test	:	Chinese hamster ovary (CHO) cells
concentration	:	125, 250, 500, 750, 1000, 1500, and 2000 ug/mL without metabolic activation and 250, 500, 1250, 2500, 3750, and 5000 ug/mL with metabolic activation.
Cycotoxic concentr.	:	4980 ug/mL
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1996
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The objective of this in vitro assay was to evaluate the ability of the test material to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, with and without metabolic activation.

Remark : A range-finding assay was also conducted wherein concentrations of 0.166, 0.498, 1.66, 4.98, 16.6, 49.8, 166, 498, 1660, and 4980 ug/mL were tested. In the non-activation assay, complete cytotoxicity was observed in the cultures dosed with 4980 ug/mL, and reductions of 100% in the mitotic index, as compared with the solvent control cultures, were observed in the culture dosed with 1660 ug/mL. In the activation assay, reductions of 19%, 33%, 27%, and 63%, as compared with the solvent control cultures, were observed in the cultures dosed with 166, 498, 1660, and 4980 ug/mL, respectively.

In the confirmatory trial, replicate cultures of CHO cells were incubated with 125, 249, 498, 746, 995, 1490, and 1990 ug/mL without metabolic activation and with 249, 498, 1250, 2490, 3730, and 4970 ug/mL with metabolic activation in 20.0 and 44.1 hour assays. Cultures treated with 746, 995, 1490, and 1990 ug/mL from the 20.0 hour assay and with 249, 498, 746, and 995 ug/mL from the 44.1 hour assay without metabolic activation, and with 1250, 2490, 3730, and 4970 ug/mL from the 20.0 and 44.1 hour assays with metabolic activation were analyzed for chromosomal aberrations. No significant increase in cells with chromosomal aberrations was observed in the non-activation assay. A significant increase in cells with chromosomal aberrations was observed in the cultures dosed with 4970 ug/mL in the 20.0 hour assay with metabolic activation. A significant increase in percent polyploidy was observed in the cultures dosed with 4970 ug/mL in the 44.1 hour assay with metabolic activation. This positive response was investigated under non-activation conditions by treating cells for 3 hours under the same conditions as the assay with metabolic activation.

In this repeat trial, replicate cultures of CHO cells were incubated with 250, 500, 1250, 2490, 3740, and 4980 ug/mL without metabolic activation for 3 hours and harvested 20.0 and 44.0 hours after initiation of treatment. Cultures treated with 250, 500, 1250, and 2490 ug/mL from the 20.0 hour assay and with 500, 1250, 2490, and 3740 ug/mL from the 44.0 hour assay were analyzed for chromosomal aberrations. No significant increase in cells with chromosomal aberrations was observed in the 20.0 hour assay. A weakly significant increase in cells with chromosomal aberrations was observed in the cultures dosed with 3740 ug/mL in the 44.0 hour assay. A significant increase in percent polyploidy was observed in the cultures dosed with 3740 ug/mL in the 44.0 hour assay.

Result : In a chromosome aberration assay in CHO cells, with multiple harvests, APFO was considered weakly positive for inducing chromosomal aberrations in CHO cells without metabolic activation with a 3-hour treatment. APFO was considered positive for inducing chromosomal aberrations in CHO cells with metabolic activation. APFO was considered positive for inducing polyploidy with and without metabolic activation.

Type	:	other: Human hepatoma HepG2 cells
System of testing Test	:	
concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS
Method	:	The genotoxic potential of PFOA was investigated in human hepatoma HepG2 cells in culture using single cell gel electrophoresis (SCGE) assay and micronucleus (MN) assay. In order to clarify the underlying mechanism(s), the intracellular generation of reactive oxygen species (ROS) was measured using dichlorofluorescein diacetate as a fluorochrome. The level of oxidative DNA damage was evaluated by immunocytochemical analysis of 8-hydroxydeoxyguanosine (8-OHdG) in PFOA-treated HepG2 cells.
Result	:	PFOA at 50-400 uM caused DNA strand breaks and at 100-400 uM micronuclei in HepG2 cells both in a dose-dependent manner. Significantly increased levels of ROS and 8-OHdG were observed in these cells. It is concluded that PFOA exerts genotoxic effects on HepG2 cells, probably through oxidative DNA damage induced by intracellular ROS.
Test substance	:	PFOA

05.12.2005 (647)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	other: Crl:CD-1 (ICR) BR
Route of admin.	:	gavage
Exposure period	:	One dose
Doses	:	200, 400, and 800 mg/kg
Result	:	negative
Method	:	other
Year	:	1996
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The objective of this in vivo assay was to evaluate the ability of the test article to induce micronuclei in bone marrow polychromatic erythrocytes of mice. This study was conducted using modifications of the procedures suggested by Heddle, J. A., Hite, M., Kirkhart, B., Larsen, K., MacGregor, J. T., Newell, G. W., and Salamone (1983). The induction of micronuclei as a measure of genotoxicity. Mutat. Res., 123:61-118. Groups of 10 male and 10 female mice were administered by gavage 200, 400, or 800 mg/kg of APFO. The animals were sacrificed at 24, 48, and 72 hours after dosing for extraction of their bone marrow.
Result	:	APFO did not induce a significant increase in micronuclei in bone-marrow polychromatic erythrocytes and is considered negative in this assay.
Test condition	:	There were 10 male and 10 female mice in the test and in the vehicle and positive control groups. Dose selection was determined in a range-finding study wherein groups of 3 male and 3 female mice were administered by gavage 200, 400, 600,

800, or 1000 mg/kg. Deaths occurred in the 1000 mg/kg group only. Signs of toxicity (hypoactivity, lacrimation, hunched posture) were seen in the 600, 800, and 1000 mg/kg groups. Based on these results in this range-finding study, the dose levels for the main study were 200, 400, and 800 mg/kg.

05.12.2005 (133)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : other: Crl:CD-1 (ICR) BR
Route of admin. : gavage
Exposure period : One dose
Doses : 498, 995, and 1990 mg/kg
Result : negative
Method : other
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this in vivo assay was to evaluate the ability of the test article to induce micronuclei in bone marrow polychromatic erythrocytes of mice. Groups of 5 male and 5 female mice were administered by gavage 498, 995, and 1990 mg/kg of APFO. The animals were sacrificed at 24, 48, and 72 hours after dosing for extraction of their bone marrow.

Remark : In a dose-selection study, APFO was solubilized in deionized water and dosed by oral gavage at 1000, 1510, 2010, 2540, and 3010 mg/kg in a first trial and then dosed at 1010, 1520, 2020, and 2530 mg/kg in a second trial. Six animals (3 males and 3 females) were assigned to each dose group. Animals were observed for 4 days after dosing for toxic signs and/or mortality.

Based on the results of the dose-selection study, the maximum tolerated dose was estimated as about 2000 mg/kg.

Result : APFO did not induce a significant increase in micronuclei in bone-marrow polychromatic erythrocytes and is considered negative in this assay.

05.12.2005 (136)

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. Post : Daily
exposure period : None
Doses : 30 or 300 ppm
Result : ambiguous
Control group : yes, concurrent no treatment
Method : other
Year : 1987
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The purpose of this study was to assess the potential toxicity and oncogenicity of APFO mixed in the diet and fed to 50 Sprague-Dawley male and 50 Sprague-Dawley female rats for 2 years. An interim sacrifice and evaluation was performed at one year on 15 additional rats per sex from the control and high-dose groups.

A total of 360 male and 360 female rats were assigned to 3 experimental groups. The APFO-treated groups were fed diets containing either 30 or 300 ppm APFO for 2 years, while a control group received only untreated feed.

In-life observations performed during the course of the study included: daily observations for abnormal signs; periodic physical examinations; body weight and feed consumption; ophthalmoscopic examinations; and clinical pathology including hematology, clinical chemistry, and urinalysis.

Macroscopic postmortem examinations were performed on all animals that died or were terminated prior to the end of the scheduled dosing. Selected organ weights were obtained from all of the rats necropsied at one year as well as from 15 rats/sex/group, randomly selected from the control and both APFO-treated groups, at the termination of the study. Selected tissue specimens were harvested from each animal at necropsy, and preserved for future histopathologic examination. Microscopic evaluation was performed on all tissues saved from all of the control and high-dose rats, while a similar evaluation was performed on a modified list of tissues obtained from the low-dose animals.

Remark : The incidence of tumors in this study was examined independently by another pathologist with the following findings (DuPont, 1987).

All of the liver tumors found in the above study were carcinomas and the incidence in the control, 30 ppm, and 300 ppm groups (males: 3/50, 1/50, 5/50; females: 0/50, 0/50, 1/50) did not appear to be dose related. The incidence of nodular hyperplasia in the liver (males: 1/50, 0/50, 2/50; females: 0/50, 0/50, 3/50) was also slightly increased, though not statistically significantly.

The incidence of testicular Leydig cell adenomas (0/50 (0%), 3/50 (6%), 7/50 (14%)) was also suggestive of a compound-related effect. When compared to Haskell's control incidence for this strain of rat (6.1%, range 1-12%), the incidence in the 300 ppm group shows a statistically significant increase.

The incidence of mammary gland fibroadenomas (10/50 (20%), 19/50 (38%), 21/50 (42%)) suggested a compound-related effect. However, when compared to Haskell's historical control incidence for this strain of rat (37%), there does not appear to be any compound-related effect.

Result : The average daily dose of APFO for both sexes was 1.5 or 15 mg/kg/day for the 30 and 300 ppm groups, respectively. The major in-life finding associated with APFO administration consisted of a dose-dependent decrease in mean body weight gain and a treatment-related increase in food consumption in males. There was no increase in mortality observed in either treatment group when compared to the control population. APFO-related hematologic changes seen in the treated rats consisted of decreased red blood cell counts, hemoglobin, and hematocrit values seen at various times throughout the two-year test period. While the decreases in erythrocyte counts were observed very early in the study, this condition did not progress into a generalized anemia by the end of the 2-year study.

Histopathologically, APFO associated toxic changes were found in the liver. These changes were characterized by increased liver weights, increased size of the liver cells with vacuolation of the cytoplasm, and some evidence of hepatocellular degeneration with occasional signs of necrosis. As with the red blood cell findings, these liver changes were noted early in the study and showed very little evidence of progression over the remainder of the 2-year study.

The incidence of tumors found in this study, with the exception of leydig cell

adenomas, was relatively low and the types of neoplasms found were not different from the tumor profiles commonly found in geriatric rats. Hepatocellular tumors were very slightly increased in the high-dose male rats; however, not to the extent that would be expected considering the morphological evidence of chronic hepatocellular stimulation first seen at the one-year necropsy.

Test condition : There were 120 male and 120 female rats in the control and test groups. An interim sacrifice and evaluation was performed at one year on 15 male and 15 female rats from the control and high-dose groups.

06.12.2005 (195) (525)

Species : rat
Sex :
Strain :
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. Post : Daily
exposure period : None
Doses : 300 ppm
Result :
Control group : yes, concurrent no treatment
Method : other
Year : 2000
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Male rats were administered either 0 (ad libitum control group (control)), 0 (control pair-fed to the APFO group, or 300 ppm APFO in the diet for approximately 2 years. After assignment to treatment groups each rat was designated for either hormonal evaluation (10/group/time point), cell proliferation evaluation (6/group/time point), or evaluation of peroxisome proliferation (6/group/time point).

All rats were provided food and tap water ad libitum. Stability of APFO was confirmed by analyses at the beginning, middle, and end of the study. Throughout the study, concentration of the test compound in the diet and the homogeneity of the test diets were determined. All rats were approximately 49 days of age on the day of study start. Body weights, food consumption, and clinical signs were monitored throughout the study.

Blood was collected for hormonal analyses at approximately 1, 3, 6, 9, 12, 15, 18, and 21 months after initiation of the study. Serum was analyzed for testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin concentrations.

Rats were sacrificed at the following interim time points: 1, 3, 6, 9, 12, 15, 18, and 21 months for cell proliferation and peroxisome proliferation evaluations.

The following organs were weighed: testes, epididymides, accessory sex gland (ASG) unit with fluid, coagulating gland/seminal vesicle with fluid removed, prostate, and liver. Immediately after weighing, the liver and testes from animals selected for peroxisome proliferation evaluation were placed in ice-cold homogenization buffer for peroxisomal preparation.

The following tissues were collected from the rats selected for cell proliferation evaluation: right and left testes, epididymides, ASG, liver, duodenum, pituitary, and all organs with gross lesions. All rats surviving the 24-month test period were sacrificed and necropsied. Brain, heart, liver, spleen, kidneys, ASG unit, coagulating gland/seminal vesicles with fluid removed, prostate, epididymides, and testes were weighed at necropsy. The liver, testes, epididymides, pancreas, and organs with gross lesions

were examined microscopically.

Data were analyzed by appropriate statistical methods.

Result : Increased relative liver weights were observed in the APFO-treated rats. Hepatic beta-oxidation activity was also increased in the APFO-treated rats at all time points. APFO did not significantly alter the rate of Leydig cell beta-oxidation or Leydig cell proliferation. Moreover, the rate of beta-oxidation in Leydig cells was approximately 20-times less than the rate of hepatic beta-oxidation.

Serum testosterone, FSH, prolactin, and LH levels were unchanged. There were, however, significant increases in serum estradiol levels in the APFO-treated rats at 1, 3, 6, 9, 15, 18, and 21 months. At 12 months, the APFO-treated rats had elevated serum estradiol levels when compared to the pair-fed control.

Histopathological evaluation revealed compound-related increases in liver, Leydig cell, and pancreatic acinar cell tumors. The Leydig cell tumors appear to be due to the combination of elevated estradiol levels and reduced prolactin levels.

APFO was included in a mechanistic bioassay investigating extrahepatic tumor induction by compounds which induce peroxisome proliferation. In this study, 300 ppm of APFO was fed to rats for two years. Increased incidences of combined (single, multiple) hepatic adenomas (10/76 versus 2/80 in ad libitum controls and 3/79 in pair-fed controls), Leydig cell adenomas (8/76 versus 0/79 and 2/78 in control groups), and combined pancreatic acinar cell adenomas (7/76 versus 0/80 and 1/79 in control groups) were noted. The tumor incidences were outside the historical control incidence range for Haskell Laboratory, and in addition, age-adjustment statistics also supported the conclusion that the tumor incidences were elevated for the liver, pancreas, and testis.

06.12.2005 (198) (205) (257)

Species : rat
Sex :
Strain :
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. Post : Daily
exposure period : None
Doses : 300 ppm
Result :
Control group : yes, concurrent no treatment
Method : other
Year : 2003
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : As part of study investigating the relationship between peroxisome-proliferating compounds and tumorigenesis in the rodent liver, testis, and pancreas, male CD rats were exposed to APFO for 2-years at dietary concentrations of 300 ppm (Biegel et al., 2001). This study was conducted at DuPont's Haskell Laboratory during 1991 and 1992. Among me findings in that study were increased incidences of pancreatic acinar cell hyperplasia and adenoma in APFO-treated rats. These results were in apparent contrast to a previous chronic feeding study with APFO in which the same rat strain was exposed to the same dietary concentration of 300 ppm (3M, 1987). In that study, no compound-related proliferative lesions of the exocrine pancreas were identified. This latter study was sponsored by the 3M company and was conducted between 1981 and 1983.

In an effort to address the apparent discrepancies between the two studies, the following activities were undertaken sequentially:

Slides of the pancreas from the 3M study were reviewed by Dr. Steven R. Frame, a veterinary pathologist at DuPont (the study pathologist for the DuPont Study). This review focused on slides from male rats in the control and 300 ppm (high dose) groups of the 3M study.

At the request of 3M, pancreas slides (control and treated) from the DuPont study were reviewed by Dr. Ernest E. McConnell, a consulting veterinary pathologist.

Dr. McConnell then reviewed all pancreas slides from the 3M study.

Drs. Frame and McConnell jointly reviewed selected pancreas slides from both the 3M and DuPont studies. This review included pancreas slides from the DuPont study stained with 5-bromo-2'-deoxyuridme (BrdU) to detect increased cell proliferation.

The slide reviews outlined above were conducted to help clarify the findings relative to pancreatic acinar cell lesions in the two chronic feeding studies with APFO. These reviews were not, however, designed as exhaustive pathology peer reviews. Thus, not all slides from all groups were examined but only those deemed necessary to assess and compare the effects on the exocrine pancreas in the two studies.

Result : The results of the two studies were similar in that APFO produced proliferative lesions of pancreatic acini in both studies at dietary concentrations of 300 ppm. In the 3M study, treatment-related changes were limited to slight increases in acinar cell hyperplasia. In the DuPont study, increased incidences of hyperplasia and adenoma were observed. Thus, these studies produced qualitatively similar responses in the pancreas, with the differences noted being quantitative-higher overall incidences of proliferative lesions and greater tendency for progression of lesions to adenoma were observed in the DuPont study compared to the 3M study. Since the difference between pancreatic acinar hyperplasia and adenoma in the rat is often a reflection of arbitrary diagnostic criteria (size) and not necessarily biological potential, the results of the two studies are in reasonable concordance given the experimental variables that exist between them. Although the basis for the quantitative difference observed is not known, a number of variables, especially diet, are known to modulate the proliferative response of the acinar pancreas in rats and are likely operative in the differences in degree of response seen in the two chronic studies with APFO. Despite these differences, target organ effects on the pancreas, characterized by focal proliferative lesions of pancreatic acini, were common to both the 3M and DuPont studies.

06.12.2005 (223)

Species : rat
Sex : male
Strain : other: Crl:CD BR(CD)
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. Post : Daily
exposure period : None
Doses : 300 ppm
Result :
Control group : yes, concurrent no treatment
Method : other
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Twenty-one day old male Crl:CD® BR (CD) rats were placed in stainless steel, wire mesh cages, individually housed, and quarantined for 3 weeks. The rats were released from quarantine by the laboratory veterinarian and selected for the study on the bases of body weights and freedom from clinical signs of disease or injury during the quarantine period. Rats were then divided by computerized, stratified randomization into treatment groups so that there were no statistically significant differences among group body weight means. Rats were assigned to the ad libitum control group (control), control pair-fed rats to the APFO group (CP-APFO), the 300-ppm APFO group, or the 50-ppm Wyeth-14,643 (WY) group. After assignment to treatment groups (n = 156/group), each rat was assigned a unique 6-digit number, and designated for either hormonal evaluation (10/group/time point), cell proliferation evaluation (6/group/time point), or evaluation of peroxisome proliferation (6/group/time point).

All rats were housed individually in stainless steel, wire-mesh cages during the test period. Cage-side examinations were conducted at least once daily throughout the study. At each weighing, rats were individually handled and carefully examined for abnormal behavior and/or appearance. Rats were weighed once a week during the first 3 months and once every other week for the remainder of the study. Rats pair-fed to the APFO group had food consumption determined twice per week for the first 3 weeks. The CP-APFO group then received the same amount of food consumed by the APFO-treated rats in the previous food consumption or weighing interval. Feed jars containing the mean daily food consumption were replaced daily. After the first 3 weeks, the amount of food consumed by each test group was determined weekly and, after 3 months, every 2 weeks. From these determinations and mean body weight data, mean daily food consumption, mean food efficiency, and intake of the test compounds were calculated.

Hormonal measurements.

Ten rats from each group were randomly selected at each sampling time point for hormonal analysis. Blood was collected from the tail vein approximately 1, 3, 6, 9, 12, 15, 18, and 21 months after initiation of the study. Serum was prepared and frozen until analyzed for testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin concentrations.

Pathological evaluation.

Rats were euthanized at interim time points 1, 3, 6, 9, 12, 15, 18, and 21 months. At each time point, 6 rats/group were selected for evaluations of cell proliferation and 6/group for peroxisome proliferation. Rats were euthanized by chloroform anesthesia and exsanguination. Testes, epididymides, accessory sex gland (ASG) unit with fluid, coagulating gland/seminal vesicle with fluid removed, prostate, and liver were weighed. Immediately after weighing, the liver and testes from animals selected for peroxisome proliferation evaluation were placed in ice-cold homogenization buffer for peroxisomal preparation. The following tissues were collected from rats selected for cell proliferation evaluation: testes, epididymides, ASG, liver, duodenum, pituitary, and all organs with gross lesions.

All rats surviving the 24-month test period were euthanized by chloroform anesthesia and exsanguination and were necropsied. Brain, heart, liver, spleen, kidneys, ASG unit, coagulating gland/seminal vesicles with fluid removed, prostate, epididymides, and testes were weighed at necropsy. The liver, testes, epididymides, pancreas, and organs with gross lesions were examined microscopically.

Cell proliferation evaluation.

Six days prior to euthanization at each of the time points, animals designated for cell proliferation evaluation were anesthetized by an injection of ketamine and xylazine, and 5-bromo-2'-deoxyuridine (BrdU) implanted subcutaneously. At sacrifice, tissues were collected and fixed for cell proliferation analysis. The labeling index was determined for hepatocytes and Leydig cells at each of the specified time points. Additionally, the pancreas was collected at the 9-, 12-, 15-, 18-, and 21-month time points and labeling indices for pancreatic acinar cells were determined. The duodenum was used as a positive control for staining of labeled cells. For each tissue type, one thousand cells were scored.

Peroxisomal beta-oxidation evaluation.

beta-Oxidation activity, a quantitative measurement of peroxisome proliferation, was determined using the method of Lazarow (1981). Briefly, the cyanide-insensitive beta-oxidation activity was measured using 5 µg hepatic peroxisomal protein/tube (0.5 mg protein/ml) and incubated at 37°C for 10 min with [14C]palmitoyl-CoA as the substrate. The reaction mixture contained 1 mM of potassium cyanide. The reaction was stopped by the addition of perchloric acid.

Statistical analyses.

Data were analyzed by one-way analysis of variance. When the corresponding F test for differences among test groups was significant, pairwise comparisons were made with the Dunnett's test ($p < 0.05$). The Bartlett's test for homogeneity of variance was also performed and if significant ($p < 0.005$), was followed by nonparametric procedures. Nonparametric procedures included the Kruskal-Wallis test for equal medians and the Mann-Whitney U test for pairwise comparisons ($p < 0.05$).

Result : WY and APFO belong to a diverse class of compounds which have been shown to produce hepatic peroxisome proliferation in rodents. From previous work, WY, but not APFO, has been shown to produce hepatocellular carcinoma in rats, while APFO has been shown to produce Leydig cell adenomas. In addition, based on a review of bioassay data a relationship appears to exist between peroxisome-proliferating compounds and Leydig cell adenoma and pancreatic acinar cell hyperplasia/adenocarinoma formation. To further investigate the relationship between peroxisome-proliferating compounds and hepatic, Leydig cell, and pancreatic acinar cell tumorigenesis, a 2-year feeding study in male CD rats was initiated to test the hypothesis that peroxisome proliferating compounds induce a tumor triad (liver, Leydig cell, pancreatic acinar cell), and to examine the potential mechanism for the Leydig cell tumors. The study was conducted using 50 ppm WY and 300 ppm APFO. The concentration of WY in the diet was decreased to 25 ppm on test day 301 due to increased mortality. In addition to the ad libitum control, a second control was pair-fed to the APFO group. Interim sacrifices were performed at 1- or 3-month intervals. Peroxisome proliferation measured by beta-oxidation activity and cell proliferation were measured in the liver and testis at all time points and in the pancreas beginning at the 9-month time point (cell proliferation only). Serum hormone concentrations (estradiol, testosterone, LH, FSH, and prolactin) were also measured at each time point. Increased relative liver weights and hepatic beta-oxidation activity were observed in both the WY- and APFO-treated rats at all time points. In contrast, hepatic cell proliferation was significantly increased only in the WY-treated group. Neither WY nor APFO significantly altered the rate of Leydig cell beta-oxidation or Leydig cell proliferation when compared to the control groups. Moreover, the basal rate of beta-oxidation in Leydig cells was approximately 20 times less than the rate of hepatic beta-oxidation. There were no biologically meaningful differences in serum testosterone, FSH, prolactin, or LH concentrations in the WY- and APFO-treated rats when compared to their respective controls. There were, however,

significant increases in serum estradiol concentrations in the WY- and APFO-treated rats at 1, 3, 6, 9, 15, 18, and 21 months. At 12 months, only the APFO-treated rats had elevated serum estradiol concentrations when compared to the pair-fed control. Histopathological evaluation revealed compound-related increases in liver, Leydig cell, and pancreatic acinar cell tumors in both WY- and APFO-treated rats. The data support the hypothesis that the peroxisome-proliferating compounds induce the previously described tumor triad. In addition, both APFO and WY produced a sustained increase in serum estradiol concentrations that correlated with the potency of the 2 compounds to induce Leydig cell tumors (i.e., WY caused a more consistent sustained increase in serum estradiol throughout the entire study, and more specifically at the end of the study, than did APFO). This study suggests that estradiol may play a role in enhancement of Leydig cell tumors in the rat, and that peroxisome proliferators may induce tumors via a non-LH type mechanism.

06.12.2005 (91) (126)

Species	:	rat
Sex	:	female
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm. Post	:	Daily
exposure period	:	None
Doses	:	30 and 300 ppm
Result	:	
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	2004
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : The slides from the ovaries from FC-143 Two-Year Oral Toxicity-Oncogenicity Study in Rats were peer reviewed by two veterinary pathologists: Peter C. Mann, DVM, Diplomate, American College of Veterinary Pathologists and Steven R. Frame, DVM, Ph.D, Diplomate, American College of Veterinary Pathologists. The slides were originally examined and reported by Dr. Robert Geil (study pathologist) for Riker Laboratories, Inc., 3M (Project Number: 0281CR0012). The peer review focused on proliferative lesions of the ovary. The peer review pathologists discussed issues related to diagnostic nomenclature and criteria and reached agreement on lesion diagnoses and grading, as well as interpretation of the peer review findings.

Result : The slides of ovaries of rats from a two-year feeding study with APFO were peer reviewed with emphasis on proliferative lesions of the ovary. Lesions diagnosed by the peer review pathologists as gonadal stromal hyperplasia or gonadal stromal adenoma corresponded to the diagnoses of tubular hyperplasia or tubular adenoma by the study pathologist (one granulosa cell tumor, a type of gonadal stromal tumor-was also diagnosed by the study pathologist). The diagnostic terms used by the peer review pathologists were based on more recently published nomenclature, and the more generic designation of gonadal stromal lesions better reflected the spectrum of morphologic changes observed in the proliferative lesions. Furthermore, based on current diagnostic nomenclature, tubular hyperplasia or adenoma would suggest an origin from ovarian surface epithelium rather than from ovarian stromal cells.

Except for differences in diagnostic nomenclature, results of the peer review were similar to those of the original study for the 300 ppm group. More disparate results occurred for the control and 30 ppm groups where more hyperplastic lesions (irrespective of the nomenclature used) were observed by the peer review pathologists. Based on the results of the peer

review, there were no statistically significant increases in gonadal stromal hyperplasia, adenoma, or adenoma and hyperplasia combined in treated groups relative to controls. Some evidence of increased lesion grade, which would correspond to an increase in size of stromal lesions, was observed in the 300 ppm group. However, adenomas occurred in greater incidences in the control group than in either of the treated groups.

06.12.2005 (230)

Species : rat
Sex :
Strain : Wistar
Route of admin. : oral feed
Exposure period : 12 months
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.005 or 0.02%
Result : positive
Control group : yes, concurrent no treatment
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : The aim of this study was to test for the ability of PFOA to act as a positive modulator of hepatocarcinogenesis, in the so-called biphasic (initiation by diethylnitrosamine 200 mg/kg ip followed by treatment with the suspected modulators) and triphasic protocols of liver carcinogenesis (initiation by the same dose of diethylnitrosamine followed by a selection procedure for 2 weeks consisting of giving 2-acetylaminofluorene and in the middle of this treatment a single dose of CCl4 followed by treatment with the suspected modulators). In the biphasic study, PFOA was fed in the diet (0.005 or 0.02%) for up to 12 months following the initiation phase. An interim sacrifice was conducted after 3 months of PFOA administration. The remaining rats were then sacrificed and the livers examined. In the triphasic study, PFOA was fed in the diet (0.015%) for 7 months following the initiation phase. Rats were then sacrificed and the livers examined. Controls were either fed the basal diet or phenobarbital (PB) [positive control].

Result : In both protocols treatment with PFOA increased the incidence of malignant hepatocellular carcinoma (HCC).

Biphasic protocol

Treatment	# Rats bearing hepatocellular carcinoma
Basal diet	0/7
0.05% PB	2/7
0.005% PFOA	1/7
0.02% PFOA	5/9

Triphasic protocol

Treatment	# Rats bearing hepatocellular carcinoma
Basal diet	0/7
0.05% PB	6/8
0.015% PFOA	4/12

As compared to phenobarbital, the modulating effect of PFOA is more pronounced in a biphasic than in the triphasic protocol. In parallel with positive modulation of HCC, PFOA also selectively induced the peroxisomal acyl-CoA oxidase activity and, to a lesser extent, catalase

activity.

Test substance : PFOA

18.10.2005 (64) (65)

Species : rat
Sex : no data
Strain : Wistar
Route of admin. : oral feed
Exposure period : 7 months
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.015%
Result : positive
Control group : yes, concurrent no treatment
Method : other
Year : 1990
GLP : no data
Test substance : other TS

Method : Using an initiation--selection--promotion protocol for induction of liver tumors in Wistar rats, the modulating action of various peroxisome proliferators on neoplasia as well as on selected biochemical parameters was studied. After treatment with diethylnitrosamine (DEN), the animals were subsequently subjected to a selection procedure involving feeding of 2-acetylaminofluorene (2-AAF), and in the middle of the 2-AAF treatment, a single necrogenic dose of carbon tetrachloride. Following a recovery period, the rats were fed a diet containing 0.1% nafenopin (NAF), 0.015% PFOA, 0.05% 2,4-dichlorophenoxyacetic acid (2,4-D), 0.05% 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) or 0.05% phenobarbital (PB) as a positive control. The animals were killed, 7 months after initiation and their livers examined.

Result : The incidence of hepatocellular carcinoma was 83, 33 and 16% in the animals treated with NAF, PFOA or 2,4,5-T respectively. No cancers were observed in controls, or in the 2,4-D groups. In comparison with controls, NAF and PFOA caused a 60-and 24-fold increase in the peroxisomal beta-oxidation of fatty acids respectively, but only about a 2-fold increase in the catalase activity, 2,4-D and/or 2,4,5-T were much less active in this respect, giving approximately a doubling in the rate of fatty acid oxidation. The specific activity of D-amino acid and glycolate oxidases were significantly depressed, whereas the urate oxidase levels were apparently unaffected by the NAF and PFOA treatment. The results suggest that the selective induction of peroxisomal fatty acid oxidation is consistent with the hypothesis that imbalance between H2O2 overproduction and its destruction could play a role in the modulation of hepatocarcinogenesis by peroxisome proliferators.

Test substance : PFOA

06.12.2005 (66) (527)

Species : rat
Sex : no data
Strain :
Route of admin. : oral feed
Exposure period : 25 weeks
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.005 or 0.02%
Result : positive
Control group : yes, concurrent no treatment
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : The aim of the present study is, first, to investigate whether the peroxisome proliferator PFOA possesses inherent liver cancer promoting activity, and second, to study the possible mechanisms involved. To achieve these aims two protocols have been applied, a biphasic protocol (initiation by diethylnitrosamine (DEN) 200 mg/kg i.p. followed by treatment with 0.005% or 0.02% PFOA for 14 and 25 weeks) and a triphasic initiation, selection-promotion protocol (initiation by giving 200 mg/kg DEN i.p. followed by a selection procedure for 2 weeks consisting of giving 0.03% 2-acetylaminofluorene (2-AAF) in diet). In the middle of this treatment a single oral dose of carbon tetrachloride (2.0 mL/kg) was given, followed by giving diet containing 0.015% of PFOA for 25 weeks.

Result : After applying both protocols, a slight increase in the catalase activity was reported while acyl CoA oxidase activity was markedly increased. Both experiments indicated that PFOA has a liver cancer promoting activity. Other groups of rats were given either basal diet or diet containing 0.02% PFOA. Five or nine weeks later they were sacrificed and the levels of 8-hydroxydeoxyguanosine in the isolated DNA were estimated. The data showed a slight nonetheless insignificant increase in 8-hydroxydeoxyguanosine. From the present data, it is concluded that PFOA is a true liver cancer promoter that may not require extensive initial DNA damage for its promoting activity.

Test substance : PFOA

06.12.2005 (63)

Species : rat
Sex : male
Strain : Wistar
Route of admin. : oral feed
Exposure period : 7 months
Frequency of treatm. Post : Daily
exposure period :
Doses : 0.015%
Result : positive
Control group : yes, concurrent no treatment
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : The initiation-selection-promotion protocol used consisted of initiation by a single dose of diethylnitrosamine (200 mg/kg) followed by a selection phase, 2 weeks later, consisting of feeding a diet containing 0.03% 4-acetylaminofluorene for 2 weeks and in the middle of this treatment a necrogenic dose of carbon tetrachloride (2 mg/kg) given in corn oil by gavage. One week after the end of the selection period 12 rats were placed on a diet containing 0.015% PFOA, another group consisting of 7 animals received nafenopin at 0.1%, whereas a control group of 10 rats received a basal diet only. Seven months after initiation, the rats were sacrificed by decapitation and livers removed and used for histological and biochemical analysis.

Result : PFOA was investigated in the initiation-selection-promotion protocol described under Methods. No tumors were found in the controls submitted solely to the initiation and selection process, although mixed noduli and loci were present. PFOA had a clear promoting action, as demonstrated by a 33% incidence of carcinomas (4/12). Nafenopin-treated animals also exhibited a high incidence of tumors with about 86% of the rats (6/7) exhibiting well differentiated hepatocellular carcinomas, but with a comparatively low incidence of foci and nodules. Biochemical analysis demonstrated, that the treatment by PPs had resulted in peroxisomal proliferation in as much as nafenopin and PFOA resulted in 60- and 24-fold specific increases, respectively, in peroxisomal acyl-CoA oxidase activities

in comparison to controls. As judged by the dicarboxylyl-CoA oxidase activities, beta-oxidation of fatty acids was also greatly increased. Whereas the level of triglycerides was significantly lower in livers from animals treated with nafenopin, there was some decrease of this parameter after animals exposed to PFOA. However, this depression was not statistically significantly lower than for controls.

Test substance : PFOA

06.12.2005 (454)

06.12.2005

5.8.1 TOXICITY TO FERTILITY

Type : other: Reproductive hormones determined in production workers
Species : human
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatm. :
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses :
Control group :
Method : other
Year : 1998
GLP : no data
Test substance : other TS

Method : Two cross-sectional studies were conducted of 111 and 80 production workers, respectively, and specifically measured their serum PFOA in relation to several reproductive hormones to determine whether such an effect occurs in humans.

Result : PFOA was not significantly associated with estradiol or testosterone in either year's study. A 10% increase in mean estradiol levels was observed among employees who had the highest levels of serum PFOA, although this association was confounded by body mass index. Neither was PFOA consistently associated with the other measured hormones. These results provide reasonable assurance that, in this production setting, there were no significant hormonal changes associated with PFOA at the serum levels measured. Limitations of this investigation include its cross-sectional design, the few subjects exposed at the highest levels, and the lower levels of serum PFOA measured, compared with those levels reported to cause effects in laboratory animal studies.

Test substance : PFOA

19.10.2005 (476)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : other: Crl:CD®(SD)BR
Route of admin. : inhalation

Exposure period	:	Days 6-15 of gestation
Frequency of treatm.	:	6 hours a day
Duration of test	:	21 days
Doses	:	0.14, 1.2, 9.9, and 21 mg/m3
Control group	:	yes, concurrent no treatment
Method	:	other
Year	:	1982
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of pregnant rats were exposed for six hours a day on days 6-15 of gestation to 0.14, 1.2, 9.9, or 21 mg/m3 of APFO. The rats were exposed whole body. Chamber concentrations of APFO were determined by gravimetric analysis either every 30 minutes (intermediate and high levels) or every 60 minutes (low level), and by a spectrophotometric technique (on each low level sample and on 5-6 samples per exposure day for the intermediate and high levels). A cascade impactor was used to determine particle size attained only for the high concentration group on the first and tenth exposure days.

Control rats were exposed to in-house air in the same type of chamber for the same duration of gestation. The dams were weighed on the day of arrival, before breeding, and on days 1, 6, 9, 13, 16, and 21 of gestation. They were observed for clinical signs and changes in demeanor upon arrival, at breeding, and daily from days 6-21 of gestation. Feed consumption was measured during gestation. The dams were coded, from before sacrifice by cervical dislocation on day 21 of gestation, until all maternal and fetal data were collected and until all structural alterations noted among the fetuses were classified, so that personnel involved did not know the exposure group to which any dam or fetus belonged. After sacrifice, the dams were examined for gross pathological changes, liver weight was recorded, and reproductive status was determined. The number of corpora lutea and implantation sites were counted, and the number and position of all live, dead, and resorbed fetuses were recorded. The uterus of each apparently "non-pregnant" rat was stained with ammonium sulfide to detect very early resorptions; data collected were used only to determine the incidence of pregnancy. The weight of the intact and empty uterus for each dam was recorded to allow calculation of actual maternal gain in body weight.

All live and dead fetuses were weighed and sexed externally and internally, and the live fetuses were examined at a magnification of 2.5X (Ednalite) for external alterations. The Ednalite also was used to count corpora lutea.

About one-half of the fetuses of each litter that were alive when removed from the dam were examined for visceral alterations; in addition, all stunted or malformed fetuses also were examined similarly. The heads of all fetuses examined for visceral alterations were fixed in Bouin's solution to permit examination, but only those from the 21 mg/m3 and control groups were sectioned free-hand and examined under a stereoscope. This included examination of a vertical cross-section through the center of the eyes as well as of one in front of the eyes and another through the widest portion of the head. Sections containing the eyes of three fetuses from each litter of the 21 mg/m3 group and of two fetuses from each litter of the control group were processed histologically for examination.

All fetuses, except for the heads of those that were fixed in Bouin's solution, were fixed in 70% ethanol, eviscerated (if not done previously), macerated in 1% aqueous KOH solution, and stained with alizarin red S to permit examination for skeletal alterations. On an as-indicated basis at sacrifice, some tissues were fixed in Bouin's solution for storage or for histologic evaluation.

Remark : In the published version of this study, slightly different exposure concentrations were reported [0.13, 1.1, 10, and 21 mg/m3].

Result : Maternal deaths occurred at the 21 mg/m3 concentration and overt toxicity was evident among the surviving dams and among those of the 9.9 mg/m3 group. No teratogenic response was observed in any of the exposed groups. Embryofetal toxicity was observed only in the 21 mg/m3 group. Other than a temporary reduction in the body weight of the pups from the 21 mg/m3 group, no adverse effects were seen in the offspring. The types of lens changes previously reported by 3M to EPA were detected in several fetuses. However, they were determined not to be related to APFO administration because they occurred at similar incidences among all groups including the controls. Lens clefts were determined to be postmortem artifacts that were caused by cutting through the center of the eyes in Bouin's fixed corneal sections. When the fetal eyes were bisected, the fetal nucleus of the lens (which is normally shifted anteriorally at this stage of gestation) was torn from its loose attachment to the anterior lens capsule and a void (cleft) was formed. The cleft was surrounded anteriorally by the lens capsule, laterally by lens' sutures, and posteriorally by the anterior surface of the fetal nucleus. This artifact was essentially eliminated by processing Bouin's fixed fetal heads that were trimmed on either side of the orbit instead of through the center of the eye. Examination of the eyes of offspring using focal illumination, indirect ophthalmoscopy, and, when indicated, slitlamp microscopy also did not detect APFO-related alterations. Therefore, the results obtained in this study did not confirm the teratogenicity of APFO.

Test condition : The control group was exposed to in-house air in the same type of chambers as the test animals.

06.12.2005 (191) (577)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : Days 6-15 of gestation
Frequency of treatm. : Once a day
Duration of test : 20 days
Doses : 25, 50, 75, 100, and 150 mg/kg
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 100 mg/kg bw
Method : other
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15, and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 mL/kg of body weight. The test material was suspended in corn oil and administered daily by oral intubation to groups of 6 rats on days 6 through 15 of gestation. A control group of 6 rats received only corn oil on the same days. On day 20 of gestation, the rats were killed by cervical dislocation and each uterus, including its contents, was examined immediately to determine if the animal was pregnant. Because 2 previous teratology studies at this laboratory with chemically related compounds resulted in fetuses with teratogenic changes in the lens of the eye, a few fetuses were also taken at day 20 of gestation and examined for eye abnormalities. Blood samples from 3 rats in each dose group were taken before the fist dose and at day 20 of gestation. Liver specimens were also taken from the same rats on day 20 of gestation.

Result : The oral administration of APFO at 25, 50, 75, 100 or 150 mg/kg/day to rats during days 6-15 of gestation did not result in any deaths. A toxic effect of reduced body weight gain occurred between days 6 and 9 of

gestation in the 150 mg/kg/day dose group. The 2 non-pregnant 150 mg/kg/day rats had a more severe effect on body weight on day 9 of the study than the pregnant high-dose dams. They lost a considerable amount of weight and one was observed to have urinary incontinence on days 11-13. The pregnant dams of the 25, 50, 75, and 100 mg/kg/day dose groups did not have abnormal clinical signs and gained weight at comparable levels to the control group. Four fetuses were examined from each of 4 dams in the 25 and 150 mg/kg/day dose groups for eye changes. All of the readable fetuses sectioned had eye changes consisting of one or more of the following: large lens cleft, dark streak running 1/2 to 3/4 of the way through the lens or disorganized lens fibers. The lens abnormalities occurred in the same location as those observed in the 2 previous teratology studies on chemically-related compounds. The abnormalities in this study appeared more pronounced than in the previous studies. In the previous studies, the teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fiber of the fetal nucleus. The same general morphological changes occurred in this study. No information was presented regarding the blood or liver samples that were taken.

06.12.2005 (519)

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Days 6-15 of gestation
Frequency of treatm.	:	Once a day
Duration of test	:	20 days
Doses	:	0.05, 1.5, 50, 150 mg/kg in distilled water
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 50 mg/kg bw
NOAEL teratogen.	:	= 150 mg/kg bw
Method	:	other
Year	:	1981
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15, and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 mL/kg of body weight. The test material was suspended in distilled water and administered daily by oral intubation to groups of 22 rats on days 6 through 15 of gestation. A control group of 22 rats received only distilled water on the same days. On day 20 of gestation, the rats were killed by cervical dislocation and the ovaries and uterus, including its contents, was examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately two-thirds of the fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. In order to evaluate lens findings seen under the dissecting microscope, all eye sections with findings, plus select eye sections without lens findings were inbedded in paraffin, sectioned at 5-6 microns, stained with hematoxylin and eosin and examined histologically.

Result : Groups of pregnant rats were administered 0.05, 1.5, 50 or 150 mg/kg of APFO on days 6-15 of gestation. Abnormal clinical signs were observed and deaths occurred only in the high-dose group. Three rats in the high-dose group died. All three of the rats that died were ataxic and two of the rats were pale for one or two days before death. The surviving high-dose

rats did not have abnormal clinical signs and signs of toxicity did not occur in lower-dose animals. APFO was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total, and dead fetuses, the mean number of resorption sites, implantation sites, corpora lutea, and mean fetus weights of the four APFO dose groups were not significantly different from the control. APFO did not cause compound-related abnormal gross fetal findings, nor did APFO treatment produce fetal skeletal malformations. A significant higher incidence of the skeletal finding of one sternabrae missing occurred in the high-dose group. One sternabrae missing is a minor skeletal aberration and was not considered a malformation in this study. Further, the incidence of the finding was not different among the control group and the lower three treatment groups. The incidences of skeletal findings associated with delayed ossification and rib aberrations were not different among the treatment groups and controls. Fetal lens findings were observed to occur in individual fetuses of all dose groups including the control group. The lens findings were localized to the area of the embryonal nucleus, although a variety of morphological appearances were present within the location. The range of morphological appearances as observed under the dissecting microscope included: a discoloration of the lens near the anteriocentral region extending from beneath the lens epithelium to half-way through the lens posteriorly, a cleft at the anteriocentral lens region or a combination of lens discoloration and the presence of a cleft. The lens findings observed under the dissecting microscope were interpreted histopathologically as a freehand sectioning artifact of a normal area of primary lens fiber degeneration. The cleft was a space opened up at the vestige of the lens vesicle remnant and consisted of a separation of primary lens fibers of the embryonal nucleus from the lens epithelial cells. The dark streak discoloration of the embryonal nucleus resulted from either the lens being freehand sectioned across the area of normal primary lens fiber degeneration or an artifact being created in the lens during freehand sectioning accentuating the area of normal primary lens fiber degeneration. The differences in the appearance of the lens artifact in individual fetuses and even among dose groups were largely due to the manner and frequency in which the artifact was created and the limitations inherent in visualizing the artifact under the dissecting microscope. Histologically, the lens artifact was the same in all dose groups regardless of the morphological appearance described under the dissecting microscope. APFO in utero exposed fetuses did not have compound-related changes in their lenses.

06.12.2005 (520)

Species	:	rat
Sex	:	female
Strain	:	other: Crl:CD (SD) BR
Route of admin.	:	gavage
Exposure period	:	Days 6-15 of gestation
Frequency of treatm.	:	Once a day
Duration of test	:	21 Days
Doses	:	100 mg/kg/day in corn oil
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1982
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Pregnant rats were administered 100 mg/kg/day by gavage on days 6-15 of gestation.

For Experiment 1, the dams were weighed on the day of arrival, before breeding, and on the morning of Days 1, 6, 9, 13, 16, and 21 of gestation. They were observed for clinical signs and changes in demeanor upon

arrival, at breeding, and daily from Days 6-21 of gestation. After mating, the rats were housed individually in suspended, wire-mesh, stainless steel cages. Feed consumption was measured during gestation. To prevent bias in the examination of maternal and fetal specimens, the dams were coded from just before sacrifice untill all maternal and fetal data were collected, and untill all structural alterations noted among the fetuses were classified. After sacrifice of the dams by cervical dislocation on Day 21, gross pathologic changes were sought, liver weight was recorded, and reproductive status was determined. The number of corpora lutea and implantation sites were counted, and the number and position of all live, dead, and resorbed fetuses were recorded. The uterus of each apparently "non-pregnant" rat was stained with ammonium sulfide to detect very early resorptions; data collected were used only to determine the incidence of
pregnancy. The weight of the intact and empty uterus for each dam was recorded to allow calculation of actual maternal gain in body weight. All live and dead fetuses were weighed and sexed externally and internally, and the live fetuses were examined at a magnification of 2.5X (Ednalite®) for external alterations. The Ednalite® also was used to count the corpora lutea. About one-half of the fetuses of each litter that were alive when removed from the dam were examined for visceral alterations; in addition, all stunted or malformed fetuses also were examined similarly. The heads of all fetuses examined for visceral alterations and sufficient of the remainder to total two-thirds of each litter were fixed in Bouin's solution. Two of the fetal heads of each litter that were fixed in Bouin's solution were sliced in vertical cross-section in front of the eyes, through the center of the eyes, and through the widest portion of the head. The remainder that were fixed in Bouin's solution were sectioned immediately in front of and behind the eyes (rather than through the eyes) and through the widest portion of the head. Three of the fetal heads of each litter that were fixed in Bouin's solution, but not cut through the eyes, were processed, and the eyes were examined histologically via light microscopy by a pathologist. The histologic specimens were coded for this examination, and particular emphasis was
placed upon the structural integrity of the lens. All fetuses, except for the heads of those that were fixed in Bouin's solution, were fixed in 70% ethanol, eviscerated (if not done previously), macerated in 1% aqueous KOH solution, and stained with alizarin red S to permit examination for skeletal alterations. On an as-indicated basis at sacrifice, some tissues were fixed in Bouin's solution for storage or for histologic evaluation. The identity of each fetus was retained at least till the report was written.

For Experiment II, the procedures used untill Day 21 G were the same as for Experiment I, except that the dams were weighed on Days 1, 6, and 21 G and twice between Days 9 and 16 G, feed consumption was not measured, and the identity of each offspring within litters was not retained. At least two days before expected parturition, each dam was housed in a 13" X 15" polycarbonate cage outfitted with a water bottle and a wire-mesh lid . The bedding (Bed-O-Cobs(R); 1/4" size) was changed weekly following the seventh day postpartum (Day 7 PP). The date of parturition was noted, and it was termed Day 1 PP. Each parturition day was considered to begin at 9:00 A.M. The dams were weighed and examined for clinical signs on Days 1, 7, 14, and 22 PP. For each test group, a Fertility Index (% matings resulting in pregnancy) and a Gestation Index (% pregnant resulting in live births) were calculated, and for each litter, a Viability Index (% animals born that survived to Day 4 PP and a Lactation Index (% animals alive at four days that survived to Day 22 PP) were calculated. All dams were sacrificed on Day 23 PP. The pups from each dam were counted, weighed, and examined for external alterations toward the end of Day 1 PP. Pups with adverse signs were marked for subsequent identification. Thereafter, each pup was weighed and inspected for adverse clinical signs on Days 4, 7, 14, and 22 PP. Neither standardization of litters nor cross-fostering was practiced. The eyes of the pups in both groups were examined on September 3, 1981 (between Days 27 and 31 PP). This examination was

conducted with the exposure levels coded. The eyes were first dilated with atropine and then examined in a semi-dark room by focal illumination, indirect ophthalmoscopy, and, when indicated, by slit-lamp microscopy. At sacrifice on Day 35 PP, each pup was exsanguinated after decapitation, and its eyes were removed and fixed in Bouin's solution.

Result : Maternal deaths occurred and during the dosing period, the surviving dams gained about one-third less body weight than the control dams. External, visceral, and skeletal alterations were sought, and the eyes of several fetuses of each litter in both groups were examined stereoscopically and histologically for alterations. The only finding noted that could possibly be APFO related was an increased incidence of fetuses with ossification sites on the first lumbar vertebrae versus the incidence in the control group. This difference in incidence was statistically significant only if analyzed by a one-tailed test. Its presence was probably a response to generalized stress evoked by the toxic state of the dams. The postpartum viability, growth rate, and development of the offspring from additional dams given APFO were not demonstrated to be adversely affected by the APFO administered. Criteria of development included examination of the pups for external alterations and ophthalmoscopic examination of the eyes.

Test condition : In a pretest, two non-pregnant female rats were administered APFO by gavage at 150 mg/kg/day which was the highest dose used in the preliminary study for 3M. The first rat, which weighed 278 g, showed severe clinical signs of toxicity by the fourth day and was found dead on the morning of the fifth day by which time it had lost about 40 g body weight. The second rat, which weighed 260 g, lost about 11 g by the third day. Two additional non-pregnant female rats were then given APFO at 100 mg/kg/day, the second highest dose level used for the 3M study. After five days of dosing, adverse clinical signs were not noted in one rat that lost about 6 g and were minimal in the other which lost about 14 g. On this basis, the 100 mg/kg/day dosage level was judged to be the maximum that the dams could tolerate for the planned exposure period of ten days.

06.12.2005 (183) (577)

Species : rat
Sex : female
Strain :
Route of admin. : gavage
Exposure period : Days 4-21 of gestation
Frequency of treatm. : Daily
Duration of test :
Doses : 3, 10, or 30 mg/kg/day
Control group : yes, concurrent vehicle
Method :
Year : 2005
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : This study was conducted to develop a quantitative understanding of the potential for gestational and lactational transfer of perfluorooctanoate (PFOA) in the rat. Groups of 20 time-mated female rats were dosed by oral gavage once daily at concentrations of 3, 10, or 30 mg/kg/day of the ammonium salt of PFOA (APFO) starting on gestation (G) day 4 and continuing until sacrifice along with a control dose containing no test substance. Formulations of test substance in deionized water were administered once daily by oral gavage at a dosing volume of 5 mL/kg; all formulations were adjusted for sample purity (%). The control group recovered 5 mL/kg deionized water. Upon arrival, dams were ranked on the basis of day 0G body weights and assigned to control and experimental groups by random sampling from the ranked list. The distribution resulted in mean body weights for all groups that were not statistically different. Rats in each group were then randomly assigned to each subset. Daily dosing continued until scheduled sacrifice at days 10G, 15G, 21G and

21PP. Dose volumes were adjusted daily based on body weights.

On days 10, 15, and 21G, five rats per dose level were sacrificed and blood samples were collected 2 hours post-dose. Embryos were collected on day 10G, amniotic fluid, placentas, and embryos/fetuses were collected on days 15 and 21G, and fetal blood samples were collected on day 21G. Five rats per dose level were allowed to deliver and nurse their litters, and on days 3, 7, 14, and 21 post-partum (PP) milk and blood samples of maternal and pup were collected 2h post-dose. All samples were analyzed by high- performance liquid chromatography-mass spectrometry (HPLC-MS) for PFOA concentration.

On days 10, 15, and 21G, rats assigned to the particular subset were euthanized by carbon dioxide inhalation. For each female with visible implantation sites, the intrauterine location of each embryo/fetus and implantation type (live or early resorption) were recorded. A gross examination of maternal viscera was done and blood samples from each dam were collected from the vena cava and processed to obtain plasma. On day 21G, fetuses were euthanized with an overdose injection (i.p.) of sodium pentobarbital, and fetal blood samples were taken from a transverse cut made to the carotid artery. To allow maximal detection of PFOA at all doses in the current study, samples were collected approximately 2 hours post-dose to be close to the Cmax.

Samples collected in each sub-group were as follows: 10G maternal blood and whole embryos; 15G maternal blood, amnionic fluid, placentas, and whole embryos; and, 21G maternal blood, amnionic fluid, placentas, whole fetuses and fetal blood. Maternal blood samples were collected 2 hours post-dose; other tissues were collected as soon as possible after maternal blood collection. All embryos, fetuses, placentas and fetal blood were pooled by litter.

On days 3, 7, 14 and 21PP, maternal milk and blood samples were collected at 2 hours post-dose. Dams were removed from their litters approximately 1-2 hours before blood and milk samples were collected. Dams were anesthetized by isofluorane inhalation. Blood samples were collected from the orbital sinus and dams were returned to their litters after recovery from anesthesia. On day 21PP, maternal blood samples were taken from the vena cava. In addition, one pup per litter (two at day 21PP) was randomly selected, euthanized and a blood sample taken from a transverse cut made to the carotid artery (days 3 and 7PP) or from the vena cava (days 14 and 21PP).

Milk samples were collected after the blood sample collection. Oxytocin was administered by intraperitoneal injection to promote milk ejection from the mammary gland. Approximately 2-5 minutes after injection, the dam's nipple area was washed with warm saline or water. Milk was collected from more than one mammary gland; mammary glands were changed frequently and were repeated as necessary. Milk was collected by applying pressure to the entire base of the gland, pushing milk towards the nipple and into a test tube. Pups were kept in polycarbonate pans with bedding during the milk collection procedure. On day 3PP, litters were kept warm during the absence of the dam by the use of either a circulating hot water pad, heated gel packs, or heat lamp.

All prepared biological samples were analyzed by high-performance liquid chromatography followed by mass spectrometry. Plasma, milk, and amniotic fluid samples (pooled by litter) were processed by protein precipitation.

Placenta samples (pooled by litter) were coarsely chopped using scissors, prepared, and analyzed. Fetus samples were pooled by litter and

homogenized using a Waring blender in the presence of liquid nitrogen, prepared, and analyzed.

Test formulations of PFOA were prepared and collected for uniformity of mixing/concentration verification and stability analysis three times during the dosing portion of this experiment. In addition, 0 mg/mL (control) samples were submitted for analysis with each set of samples.

Result : Concentrations of PFOA in maternal plasma and milk attained steady state during the sampling interval. The steady-state concentrations in maternal plasma were 10-15, 25-30, and 60-75 microg/mL in rats receiving 3, 10, and 30 mg/kg, respectively. Steady-state concentrations in milk were approximately 10 times less than those in maternal plasma. The concentration of PFOA in fetal plasma on day 21G was approximately half the steady-state concentration in maternal plasma. The milk concentrations appeared to be generally comparable to the concentrations in pup plasma. Pup plasma concentrations decreased from day 3PP to day 7PP, and were similar on days 7, 14, and 21PP at all dose levels. PFOA was detected in placenta (days 15 and 21G), amniotic fluid (days 15 and 21G), embryo (days 10 and 15G), and fetus (day 21G). These pharmacokinetics allow estimation of the dose to developing and nursing rat offspring following maternal exposure.

06.12.2005 (221) (320)

Species : mouse
Sex : female
Strain : CD-1
Route of admin. : gavage
Exposure period : Days 2-18 of gestation
Frequency of treatm. : Daily
Duration of test :
Doses : 1, 3, 5, 10, 20, and 40 mg/kg/day of PFOA in water
Control group : yes, concurrent vehicle
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : CD-1 mice were mated overnight and the day on which copulatory plugs were found was designated gestation day 1 (GD 1). Animals were administered by gavage 1, 3, 5, 10, 20, or 40 mg/kg/day from GD 2 to GD 18; controls received an equivalent volume of water.

Result : PFOA treatment produced early, full-litter resorptions in a dose-dependent manner, leading to 100% loss in the 40 mg/kg group. Significant deficits in maternal weight gains were detected in dams of the 20 mg/kg group that carried pregnancy to term. On GD 18, some dams were sacrificed for maternal and fetal examinations while the rest were allowed to give birth for monitoring of postnatal survival, growth, and development of the pups. PFOA induced liver enlargement in the dams at all doses, but did not alter the number of implantations. In the 20 mg/kg group, the percent of live fetuses was reduced to 74% (compared to 97% in the controls) the day before birth, and fetal weight (0.86 plus or minus 0.11 g) was significantly lower than that of controls (1.05 plus or minus 0.02 g). However, no discernible anatomical malformations were noted in any of the treatment groups. The incidence of live births was significantly lowered by PFOA in the 10 and 20 mg/kg groups (70% compared to 93% in the control group), and postnatal survival of the neonates was severely compromised in these treatment groups. Dose-dependent deficits of weight gains were detected in all PFOA-treated pups. Significant delays in eye-opening (by about 2 days) were noted in the 10 and 20 mg/kg groups, and pubertal indices were significantly delayed (by about 3 days in males and females) in the 20 mg/kg group. These data indicate maternal and developmental toxicities of PFOA in the mouse measured as early pregnancy loss, compromised

postnatal survival, and delays in postnatal growth and maturation.

Test substance : PFOA

06.12.2005 (595)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : Days 6-18 of gestation
Frequency of treatm. : Once a day
Duration of test : 29 days
Doses : 1.5, 5, and 50 mg/kg in distilled water
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 5 mg/kg bw
NOAEL teratogen. : = 50 mg/kg bw
Method : other
Year : 1982
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The animals were observed daily from days 3 through 29 of gestation for abnormal clinical signs. Body weights were recorded on gestational days 3, 6, 9, 12, 15, 18, and 29 of gestation and the rabbits dosed accordingly using a constant dose volume of 1 mL/kg of body weight. The test material was suspended in distilled water and administered daily by oral intubation to groups of 18 rabbits on days 6 through 18 of gestation. A control group of 18 rabbits received only distilled water on the same days. On day 29 of gestation, the rabbits were killed by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, fetal weights and sex, and gross fetal abnormalities. The fetuses were then placed in an incubator at 37°C for a 24-hour incubation period. Following the incubation period, all fetuses were killed and examined for internal abnormalities. The fetuses were then preserved in ethyl alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities.

Result : Groups of pregnant rabbits were administered 1.5, 5 or 50 mg/kg of APFO in distilled water on days 6-18 of gestation. At 50 mg/kg the dams lost more weight than the untreated controls. No compound-related toxic clinical signs or deaths occurred in any of the treated groups. APFO was not embryotoxic and did not affect the ovaries or reproduction tract contents of the rabbits. APFO did not cause gross, internal, or skeletal malformations of the fetuses. Statistically significant increases in the incidence of 13 ribs in the high-dose group and 13 ribs spurred in the mid-dose group were observed. While these findings are significantly greater in the dosed rabbits than in the controls, they are not considered teratogenic changes or malformations. Findings associated with skeletal ossification were not different among the four treatment groups. APFO was not teratogenic in the rabbit.

Test condition : A range-finding study determined that APFO was toxic to pregnant rabbits at dose levels of 100 mg/kg/day and higher. The toxicity resulted in deaths within the first four days of dosing. The 50 mg/kg/day rabbits survived 13 days of dosing but lost a significant amount of body weight early in the dosing interval (days 6-9 of gestation). The high dose level for a rabbit teratology study was set at 50 mg/kg/day based on these results.

06.12.2005 (522)

Species : other: In vitro study in mouse whole embryo cultures
Sex :
Strain :
Route of admin. : other: Whole embryo cultures
Exposure period : 24 hours

Frequency of treatm.	:	
Duration of test	:	
Doses	:	0.1, 0.2, 0.4, 0.6, 0.75, 1.0, and 1.25 mg/mL
Control group	:	no data specified
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : In order to determine if direct exposure of conceptuses to PFOA disrupts development, CD-1 mouse conceptuses (3-6 somite stage, GD 8) were exposed to PFOA in whole embryo culture. At the end of a 24-hour culture period, embryonic morphology was assessed and scored using a scoring system developed in this laboratory. Scores ranged from 0 for morphologically normal to a maximum of 58 for severely affected embryos.

Result : In control medium, 82% of the embryos (18/22) grew normally and the mean score was 0.4 (plus or minus 0.2). Exposure to 0.1 or 0.2 mg/mL PFOA did not alter development (4/4 and 11/17, normal embryos, respectively). However, dysmorphogenesis was induced by PFOA at 0.4 (82%), 0.6 (92%), 0.75 (100%), and 1.0 (100%) mg/mL. Exposure to 1.25 mg/mL produced 100% embryolethality. Prosencephalic and pharyngeal arch hypoplasia and abnormal heart outflow tract development were induced by greater than 0.4 mg/mL PFOA. Embryonic scores were increased at PFOA concentrations greater than 0.4 mg/mL and were 0.0, 1.7, 11.3, 11.3, 23.5, and 31.1 for the 0.1, 0.2, 0.4, 0.6, 0.75, and 1.0 mg/mL groups, respectively. The benchmark concentration for a 5% increase in dysmorphic embryos by PFOA was 0.4 mg/mL. These studies demonstrate that a direct exposure to PFOA for 24 hours disrupts development and induces embryolethality.

Test substance : PFOA

06.12.2005 (100)

Species	:	other: QSAR model of teratogenesis.
Sex	:	
Strain	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Duration of test	:	
Doses	:	
Control group	:	

06.12.2005

06.12.2005

06.12.2005

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type	:	other: Multi generation study
In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage

Exposure period	:	P-generation were dosed at least 70 days prior to mating and until sacrificed; F1-generation rats were dosed similarly, beginning at weaning; F2-generation pups through day 22 of lactatation
Frequency of treatm.	:	daily
Duration of test	:	2 generations
Doses	:	1, 3, 10, or 30 mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other: EPA OPPTS 870.3800 Guidelines
Year	:	1998
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The P generation consisted of five dosage groups, 30 rats per sex per group. Two F1-generation pups per sex per litter per group (60 per sex per group) were selected for continued evaluation (300 rats per sex total) at weaning. APFO or vehicle (water) was administered by oral gavage to the P-generation rats, beginning at 6 weeks of age and at least 70 days before cohabitation, at daily dosages of 0, 1, 3, 10, and 30 mg/kg using a constant volume of 5 ml/kg.

The F1-generation rats were individually identified and given the same dosage level and volume of the test substance as their respective sires and dams beginning at weaning (days of lactation 22-DL 22). The P- and F1-generation rats were observed for clinical observations, abortions or premature deliveries, and deaths before and 60 min post-dosage. Body weights and feed consumption values of the male and female rats were recorded weekly and on days of gestation (DG) 0, 7, 10, 14, 18, 21 and on DL 1, 5, 8, 11, 15, and 22 for the dams. Feed consumption values were not recorded during cohabitation. Feed consumption values were not tabulated after DL 15 because pups begin to consume maternal feed on or about this time.

F1-generation female and male rats were examined for age of vaginal patency or preputial separation beginning on day 28 or 29 postpartum, respectively. Body weights were recorded when rats reached sexual maturity. Following sexual maturation, 30 mating pairs were randomly selected, excluding sibling pairs, and non-selected pups were sacrificed and necropsied. Estrous cycling was evaluated by examination of vaginal cytology beginning 21 days before cohabitation and until mating. The cohabitation period was a maximum of 14 days. Evidence of mating was determined by spermatozoa observed in a vaginal smear or a copulatory plug observed in situ (DG0). On the day of sacrifice, stage of estrous was again determined. The female rats were evaluated for duration of gestation, fertility and gestation indices, number and sex of offspring, number of implantation sites, condition of dam and litter, litter size, viability index, lactation index, percent survival and sex ratio. F2-generation pup body weights were recorded on DL 1, 5, 8, 15, and 22. On DL 12 all F2-generation males were examined for the presence of nipples. Anogenital distance was measured for F2-generation pups on DL 1 and 22.

P- and F1-generation rats were euthanized by carbon dioxide asphyxiation, necropsied and examined for gross lesions. Blood samples were collected from the inferior vena cava and serum shipped frozen for APFO analysis. The brain, kidneys, spleen, ovaries, testes, thymus, liver, adrenal glands, pituitary, uterus with oviducts and cervix, left epididymis, right epididymis, prostate and seminal vesicles were individually weighed. The pituitary, adrenal glands, vagina, uterus with oviducts, cervix and ovaries, right testis (initially fixed in Bouin's solution), seminal vesicles (with coagulating glands), right epididymis and prostate were retained for histology. Histological examination was performed on tissues from 10 randomly selected rats per sex from the control and high dosage groups. All gross lesions and reproductive organs of the low and intermediate dosage group

rats with reduced fertility were histologically evaluated. Histopathological examination of the testis was conducted in order to identify retained spermatids, missing germ cell layers or types, multinucleated giant cells or sloughing of spermatogenic cells into the lumen. Examination of the intact epididymis (including the caput, corpus and cauda) was conducted in order to identify such lesions as sperm granulomas, leukocytic infiltration (inflammation), aberrant cell types within the lumen, or absence of clear cells in the cauda epididymal epithelium.

Male rats were sacrificed after cohabitation. The P-generation male rats were 106-110 days of age and the F1-generation male rats were 109-120 days of age. A portion of the left cauda epididymis was used for evaluation of cauda epididymal sperm concentration and motility using computer assisted sperm analysis (CASA). The motility was evaluated by the Hamilton Thorne IVOS. The remaining left cauda epididymis was used to manually evaluate sperm morphology. Sperm morphology evaluations included both the determination of the percentage of normal sperm (in a sample of at least 200) and qualitative evaluation of abnormal sperm. The left testis was used for evaluation of testicular spermatid concentration (10 fields) using the CASA. The left testis was weighed both before and after removal of the tunica albuginea and then homogenized; a sample from the homogenate was stained with an IDENT stain before IVOS analysis.

Female rats were euthanized by carbon dioxide asphyxiation on DL 22. The number and distribution of implantation sites were recorded. Uteri of apparently nonpregnant rats were examined while being pressed between glass plates to confirm the absence of implantation sites. All F1-generation pups culled on DL 22 were euthanized by carbon dioxide asphyxiation. Three randomly selected pups per sex per litter were examined for gross lesions. The necropsy included a single cross-section of the head at the level of the frontal-parietal suture and examination for hydrocephaly. The brain, spleen and thymus from one of the three selected F1-generation pups per sex per litter were weighed and retained for histological evaluation.

Result : Reproductive endpoints including mating, fertility, and natural delivery were not affected in either generation. P- and F1-generation male rats showed decreased body weight, and liver and kidney weight increases at all doses. The 30 mg/kg F1-generation pups had decreased birth weight. Viability was reduced in the 30 mg/kg F1-generation pups in apparent relationship to reduced body weight at birth and weaning; however, F2-generation pups at 30 mg/kg, although somewhat lighter, did not show a loss in viability. Preputial separation and vaginal opening were somewhat delayed at 30 mg/kg, but these rats went on to show normal reproductive performance. No-observed-adverse-effect-levels were >30 mg/kg for reproductive function of P- and F1-generation rats, 10 mg/kg for F1-generation pup mortality, birth weight, and sexual maturation, and less than 1 mg/kg for male body-weight and organ-weight changes.

06.12.2005 (76) (109) (111)

5.9 SPECIFIC INVESTIGATIONS

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type : other: In vitro`
Species :
Sex :
Strain :
Route of admin. :
No. of animals :

Method : other
Year : 1997
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Several peroxisome proliferators have been shown to produce pancreatic acinar cell hyperplasia/adenocarcinomas in 2-year bioassays with rats: APFO, clofibrate, methylclofenapate, HCFC-123, and Wyeth-14,643 (WY). In vitro APFO and WY and in vivo (WY) approaches were used to examine several possible mechanisms of pancreatic tumorigenesis by peroxisome proliferating compounds. These mechanisms include cholecystokinin receptor agonism (CCKA), trypsin inhibition, alterations in gut fat content, cholestasis, and altered bile flow/-composition.
Result : All of these mechanisms enhance pancreatic growth either by binding to the CCKA receptor or by increasing plasma CCK levels. In vitro experiments using a receptor competition binding assay demonstrated that WY and APFO do not bind directly to the CCKA receptor. In a continuous spectrophotometric assay, WY and APFO also failed to inhibit trypsin, a common mechanism for increasing plasma CCK levels. These in vitro results suggested that WY and APFO are not acting via the two most common mechanisms for modulation of pancreas growth.

06.12.2005 (461)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Perfluorooctane sulfonate (PFOS) and PFOA are amphiphiles found ubiquitously in the environment, including wildlife and humans, and are known to have toxic effects. The effects of PFOS and PFOA on action potentials and L-type Ca(2+) currents, I(CaL), were studied in isolated guinea-pig ventricular myocytes using whole-cell patch-clamp recording.
Result : In current-clamp experiments, PFOS significantly decreased the rate of spike, action potential duration, and peak potential at doses over 10 microM. In voltage-clamp experiments, PFOS increased the voltage-activated peak amplitude of I(CaL), and shifted the half-activation and inactivation voltages of I(CaL) to hyperpolarization. PFOA had similar effects PFOS, but showed significantly lower potency. These findings are consistent with previous observations for anionic n-alkyl surfactants, suggesting that PFOS and PFOA may change membrane surface potential, thereby eliciting general effects on calcium channels.
Test substance : PFOS and PFOA

06.12.2005 (309)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :

No. of animals :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : Perfluorooctanyl compounds with active functional groups have been shown to disrupt mitochondrial bioenergetics by three distinct mechanisms: protonophoric uncoupling of mitochondrial respiration, induction of the mitochondrial permeability transition (MPT), or a nonselective increase in membrane permeability. The purpose of this investigation was to identify the initial target and specific sequence of events associated with the N-acetyl substituted perfluorooctanesulfonamides induced MPT. N-acetylperfluorooctanesulfonamide (FOSAA), N-ethyl-N-acetyl-perfluorooctanesulfonamide (N-Et FOSAA), PFOA, perfluorooctanesulfonate (PFOS), and N-ethyl-N-(2-ethoxy)perfluorooctanesulfonamide (N-Et FOSE) were added individually to liver mitochondria freshly isolated from Sprague-Dawley rats. Mitochondrial swelling and cytochrome c release were recorded spectrophotometrically, oxygen uptake was monitored with a Clark-type oxygen electrode, and reactive oxygen species (ROS) were monitored by dichlorodihydrofluorescein diacetate (H(2)DCFDA) fluorescence.

Result : FOSAA (45 uM) and N-Et FOSAA (7.5 uM) induced calcium-dependent mitochondrial swelling, the release of cytochrome c, inhibition of uncoupled mitochondrial respiration, and ROS generation, all of which were inhibited by cyclosporin-A (CsA). PFOA (200 uM) displayed slight CsA sensitive activity, but neither PFOS (10 uM) nor N-Et FOSE (70 uM) induced the MPT. Results of this investigation demonstrate two important findings: (1) MPT induction is specific to the N-acetyl substituted perfluorooctanesulfonamides and, (2) the sequence of events is initiated by induction of the MPT, which causes the release of cytochrome c as well as other cofactors leading to inhibition of respiration and ROS generation. The toxicity of N-acetyl perfluorooctanyl compounds may therefore reflect the mitochondrial dysfunction, which is compounded by the ensuing oxidative injury.

Test substance : PFOA

06.12.2005 (458)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : 19F NMR techniques, such as, chemical shift, spin-lattice (T1), and spin-spin (T2) relaxation phenomena, coupling constants, and variable-temperature NMR were used to furnish a qualitative explanation of why increasing the carbon chain length causes unexpected intrinsic property changes within this group of polyfluorinated chemicals.

Result : Results indicate that polyfluorinated chains adopt helical twist geometry unlike their hydrocarbon counterparts which exhibit a zigzag geometry. Variable-temperature 19F NMR showed that chain rigidity within these molecules is also a function of the fluorocarbon chain length. There is a distinct change in geometry and rigidity of the acid chain between 8 and 10

carbon lengths. These unique geometric changes in this class of compound must be considered when assessing their dissemination in the environment, for example, in the case of environmental modeling.

Test substance : PFOA

06.12.2005 (248)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : no data
Strain : Fischer 344
Route of admin. : ip or oral
No. of animals :
Method : other
Year : 2001
GLP : no data
Test substance : other TS

Method : Perfluorinated fatty acids (PFFAs), such as PFOA and PFDA, are known peroxisome proliferators and hepatocarcinogens. A causal link between an increase in the oxidative stress by peroxisomes and tumor promotion has been proposed to explain the hepatocarcinogenicity of PFOA and PFDA. However, the down-regulation of gap junctional intercellular communication (GJIC) has also been linked to the tumor-promoting properties of many carcinogens. Therefore, the effect of PFFAs on GJIC in WB-rat liver epithelial cells was determined. The chain length of the PFFAs tested for an effect on GJIC ranged from 2 to 10, 16 and 18 carbons.

Result : Carbon lengths of 7 to 10 inhibited GJIC in a dose-response fashion, whereas carbon lengths of 2 to 5, 16 and 18 did not appreciably inhibit GJIC. Inhibition occurred within 15 minutes and was reversible, with total recovery from inhibition occurring within 30 minutes after the removal of the compound from the growth medium. This short time of inhibition suggests that GJIC was modified at the post-translational level. Also, this short time period was not long enough for peroxisome proliferation. The post-translational modification of the gap junction proteins was not a consequence of altered phosphorylation as determined by Western blot analysis. PFOA also inhibited GJIC in a dose-response fashion similar to PFDA, indicating that the determining factor of inhibition was probably the fluorinated tail, which required 7-10 carbons. Our results suggest that PFFAs could potentially act as hepatocarcinogens at the level of gap junctions in addition to or instead of through peroxisome proliferation. Based on these results, the inhibitory PFOA and the non-inhibitory perfluoropentanoic acid (PFPA) were studied in vivo in rats administered either a single ip dose or mixed in the feed. Similar to the above in vitro results, PFOA inhibited GJIC in rat liver tissue while PFPA had no effect on GJIC. Inhibition of GJIC with PFOA correlated with hepatomegaly but rats treated with PFPA exhibited no hepatomegaly.

Test substance : PFOA

06.12.2005 (604) (605)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : oral feed
No. of animals : 6
Vehicle :

Exposure period	:	28 day(s)
Frequency of treatm.	:	Daily
Doses	:	300 ppm
Control group	:	no data specified
Observation period	:	
Result	:	
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : In order to investigate pancreatic gene expression changes that may be associated with pancreatic carcinogenesis, male Sprague-Dawley rats were administered a diet containing 300 ppm of APFO for 4 weeks and transcriptional profiling using a rat cDNA array containing 14,000 genes was performed in pancreas and liver.

Result : 577 and 617 APFO treatment-regulated genes were identified in the pancreas and liver, respectively. 267 pancreas genes and 294 liver genes were up-regulated and 310 pancreas and 323 liver genes were down-regulated. In the liver, many of the transcriptionally induced genes were found to be regulated by the transcription factor PPAR alpha. In the pancreas, a marked up-regulation of phosphoenolpyruvate carboxykinase, a PPAR gamma-regulated gene in adipose tissue, was observed. Groups of genes involved in MAP kinase and Notch signaling together with target genes for these signaling pathways, were also up-regulated. Gene expression changes which could lead to metabolic acidosis and perturbations in glutamine metabolism and apoptosis were also observed. Examining the broad transcriptional effects of APFO in the liver generated a profile of gene expression changes indicative of increases in hepatic beta-oxidation and fat metabolism. This observation is consistent with the compound acting as a PPAR alpha agonist and peroxisome proliferator. By contrast, gene expression changes observed in the pancreas were quite different and suggested possible effects on gluconeogenesis and glutamine metabolism. The profile of regulated genes associated with carcinogenesis were indicative of metabolic acidosis, oxidative stress, and endogenous processes of DNA damage against a background of increased mitogenesis.

04.11.2005 (501)

Endpoint	:	Mechanistic Studies
Study descr. in chapter	:	
Reference	:	
Type	:	
Species	:	rat
Sex	:	
Strain	:	Fischer 344
Route of admin.	:	gavage
No. of animals	:	
Vehicle	:	other: Olive oil
Exposure period	:	
Frequency of treatm.	:	
Doses	:	100 mg/kg
Control group	:	
Observation period	:	
Result	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS

Method : The mechanism by which hypolipidemic drugs and industrial plasticizers cause hepatic tumors in rodents remains unknown. It is known, however,

that protein kinase C is elevated during hepatic cell turnover, and sustained cellular replication is correlated with an increased incidence of hepatic tumors. Therefore, several peroxisomal proliferators varying in their tumorigenic potency in chronic feeding studies were examined for their ability to increase protein kinase C activity.

Result : Intragastric administration of (4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio)acetic acid (Wy-14,643; 100 mg/kg) increased protein kinase C activity threefold in 5 hr and fivefold in 10 hr. Perfluorooctanoate also increased protein kinase C activity significantly in microsomes at 5 hr. Wy-14,643 and perfluorooctanoate also diminished acyl CoA synthetase activity significantly, with Wy-14,643 exhibiting competitive type kinetics. Other peroxisomal proliferators were examined [e.g., ciprofibrate, clofibrate, 2-ethylhexanol, valproate, and di(ethylhexyl)phthalate (DEHP)] and collectively an inverse relationship between their ability to stimulate protein kinase C activity and inhibit acyl CoA synthetase was observed (r = -0.80). All chemicals examined had no direct effect on protein kinase C activity in vitro. Interestingly, those compounds which are more potent as hepatocarcinogens (e.g., Wy-14,643) in long-term feeding studies decreased acyl CoA synthetase and elevated protein kinase C activity to a greater extent than their weaker counterparts (e.g., DEHP). It is proposed that inhibition of acyl CoA synthetase by peroxisomal proliferators elevates free fatty acids which stimulate protein kinase C activity and ultimately promote tumor formation.

Test substance : PFOA

08.11.2005 (101)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1997
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Leydig cell adenomas are observed frequently in studies evaluating the chronic toxicity of chemical agents in laboratory animals. Doubts have been raised about the relevance of such responses for human risk assessment, but the question of relevance has not been evaluated and presented in a comprehensive manner by a broad group of experts. This article reports the consensus conclusions from a workshop on rodent Leydig cell adenomas and human relevance.

Result : Five aspects of Leydig cell biology and toxicology were discussed: 1) control of Leydig cell proliferation; 2) mechanisms of toxicant-induced Leydig cell hyperplasia and tumorigenesis; 3) pathology of Leydig cell adenomas; 4) epidemiology of Leydig cell adenomas; and 5) risk assessment for Leydig cell tumorigens. Important research needs also were identified. Uncertainty exists about the true incidence of Leydig cell adenomas in men, although apparent incidence is rare and restricted primarily to white males. Also, surveillance databases for specific therapeutic agents as well as nicotine and lactose that have induced Leydig cell hyperplasia or adenoma in test species have detected no increased incidence in humans. Because uncertainties exist about the true incidence in humans, induction of Leydig cell adenomas in test species may be of concern under some conditions. Occurrence of Leydig cell hyperplasia alone in test species after lifetime exposure to a chemical does not constitute a cause for concern in a risk assessment for carcinogenic

potential, but early occurrence may indicate a need for additional testing. Occurrence of Leydig cell adenomas in test species is of potential concern as both a carcinogenic and reproductive effect if the mode of induction and potential exposures cannot be ruled out as relevant for humans. The workgroup focused on seven hormonal modes of induction of which two, GnRH agonism and dopamine agonism, were considered not relevant to humans. Androgen receptor antagonism, 5 alpha-reductase inhibition, testosterone biosynthesis inhibition, aromatase inhibition, and estrogen agonism were considered to be relevant or potentially relevant, but quantitative differences may exist across species, with rodents being more sensitive. A margin of exposure (MOE; the ratio of the lowest exposure associated with toxicity to the human exposure level) approach should be used for compounds causing Leydig cell adenoma by a hormonal mode that is relevant to humans. For agents that are positive for mutagenicity, the decision regarding a MOE or linear extrapolation approach should be made on a case-by-case basis. In the absence of information about mode of induction, it is necessary to utilize default assumptions, including linear behavior below the observable range. All of the evidence should be weighed in the decision-making process.

08.11.2005 (125)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method :
Year : 1996
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : A review of the literature indicates that some compounds which produce hepatic peroxisome proliferation in rats also appear to produce Leydig cell adenomas, and some also affect the serum concentrations of testosterone and estradiol. Previous studies with the peroxisome proliferator APFO showed a direct effect on Leydig cells to alter steroidogenesis. It was therefore proposed that peroxisome proliferators in general may directly affect Leydig cell function to produce Leydig cell tumors by some undetermined mechanism. The present study investigated whether the following peroxisome proliferators directly affect Leydig cell function in vitro: 2,4-dichlorophenoxyacetic acid, clofibric acid, APFO, acetylsalicylic acid, ciprofibrate, gemfibrozil, tiadenol, tibric acid, trichloroacetic acid, trichloroethylene, and Wyeth 14,643. Leydig cells, isolated from adult Charles-River rats (12-16 weeks old), were treated with peroxisome proliferator for 21 hours and the medium was assayed for estradiol. The function of the treated Leydig cell was evaluated by measuring the release of testosterone in response to human chorionic gonadotropin (hCG).

Result : In general, the peroxisome proliferators reduced the hCG-stimulated release of testosterone and either reduced or had no effect on the baseline release of testosterone. Of the 11 peroxisome proliferators, 8 increased the release of estradiol from Leydig cells treated for 1 day. APFO reduced the basal release of estradiol from Leydig cells treated for 1 day, but increased the release when the Leydig cells were treated for 2 or 3 days. These effects were seen at non-cytotoxic doses and at concentrations similar to those achieved in rat serum in dietary studies. The results suggest that peroxisome proliferators, as a class of compounds, directly modify the steroidogenic function of Leydig cells in vitro. Some of these compounds are known to produce Leydig cell tumors in rats, but this

association has yet to be established for other peroxisome proliferators. This suggests that compounds which directly affect Leydig cell function in vitro may also induce Leydig cell tumors in vivo. Further investigations are necessary to address the mechanism for the in vitro effects on Leydig cells and to clarify the apparent relationship between peroxisome proliferator-induced changes in Leydig cell function and the development of Leydig cell tumors.

06.12.2005 (418)

Endpoint : Mechanistic Studies
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1995
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : In the present work, APFO was examined for its ability to (1) directly affect Leydig cells in vitro using isolated Leydig cells from untreated rats and ex vivo using Leydig cells isolated from APFO-treated rats, (2) affect testicular interstitial fluid hormone levels, and (3) induce aromatase activity. These studies were conducted to investigate the hypothesis that APFO produces an increase in estradiol by inducing cytochrome P450 XIX (aromatase), which converts testosterone to estradiol, and that the elevated estradiol levels ultimately produce Leydig cell hyperplasia and adenoma formation by acting as a mitogen or enhancing growth factor secretion. In the in vivo and ex vivo studies, adult male CD rats were gavaged with either 0 or 25 mg/kg/day APFO for 14 days. In addition to the ad libitum control, a second control group was pair-fed to the 25 mg/kg/day APFO group. In the in vitro and ex vivo studies, Leydig cells were isolated from testes of adult males by collagenase digestion followed by enrichment over Percoll gradients.

Result : A dose-dependent decrease in testosterone levels was observed in hCG-stimulated Leydig cells treated in vitro with APFO for 5 hours (IC50 approximately 200 microM). In contrast, ex vivo studies demonstrated an increase in testosterone production in hCG-stimulated Leydig cells from APFO-treated rats when compared to Leydig cells isolated from either the ad libitum or pair-fed control rats. The in vitro data demonstrate that APFO directly inhibits testosterone release from Leydig cells, while the ex vivo data demonstrate that this inhibition is reversible.

06.12.2005 (92)

Endpoint : other: Ability of peroxisome proliferators to induce liver microsomal carboxyesterase
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : Differences in the ability of metabolically inert peroxisome proliferators PFDA, PFOA, perfluorooctane sulfonic acid (PFOS, C8) and 1H,1H-pentadecafluoro-n-octanol (PFOL, C8)) to induce liver microsomal carboxylesterase RL4 in male rats were studied by evaluating changes in the RL4 content by immunoblot analysis with a specific antibody.

Result : The administration of PFOA, PFOS and PFOL markedly increase the content of carboxylesterase RL4. On the other hand, PFDA decreases PNPA, BUTA, and ISOC hydrolase activity, and slightly increases the carboxylesterase RL4 content.

Test substance : PFOA

06.12.2005 (152)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1993
GLP : no data
Test substance : other TS

Method : Non-metabolizable perfluorinated butanoic (PFBA), octanoic (PFOA), and decanoic (PFDA) acids were studied in vitro to determine their ability to cause peroxisome proliferation in primary cultures of adult rat hepatocytes.

Result : Non-metabolizable perfluorinated butanoic (PFBA), octanoic (PFOA), and decanoic (PFDA) acids, unlike naturally occurring carboxylic acids, caused peroxisome proliferation in primary cultures of adult rat hepatocytes. Ciprofibrate (CIP) was used as a reference standard. PFOA, like CIP, increased peroxisome diameter and number, and cytoplasmic volume occupied by peroxisomes. Perfluorinated fatty acids and CIP produced concentration-dependent increases in microsomal laurate hydroxylase and peroxisomal fatty acyl-CoA-oxidase (FACO) activities with a rank order of potency CIP > PFOA > PFDA > PFBA. Maximal increases in FACO activity produced by PFOA were not additive with PFDA or CIP.

Test substance : PFOA

16.11.2005 (262) (336)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1998
GLP : no data
Test substance : other TS

Method : The effects of endogenous fatty acids and PFOA and its analogs on peroxisomal acyl CoA oxidase (ACO) and microsomal laurate hydroxylase (LH) activities were evaluated in primary cultures of rat hepatocytes and activation of peroxisome proliferator-activated receptor alpha (PPARalpha) in CV-1 cells.

Result : The rank order for the stimulation of ACO activity in hepatocytes for

selected compounds was PFOA >> octanoic acid > octanedioic acid, perfluorooctanol (inactive). Increases in ACO activity by PFOA, like those of ciprofibrate, were associated with a marked increase in peroxisome number and cytosolic occupancy volume. Maximal effects of ciprofibrate and PFOA on the stimulation of ACO activity were not additive, suggesting that these two compounds share a common pathway of peroxisome proliferation.

Saturated mono-carboxylic acids of C4 to C18 chain length were inactive, and, among dicarboxylic acids, only small elevations (40-45%) in ACO activity were observed with the long-chain C12 and C16 dioic acids. Of the C18 fatty acids tested, only oleic and linoleic acids, at 1 mM, produced a two- to three-fold elevation in ACO and LH activities. In comparison with endogenous fatty acids, PFOA was more potent and exhibited a different time course and greater magnitude of stimulation of ACO and LH activities in cultured hepatocytes.

Addition of mitochondrial beta-oxidation inhibitors (3-mercaptopropionic and 2-bromooctanoic acids) did not alter ACO activity in the presence of octanoic acid or octanedioic acid; nor did they modify the stimulation of ACO activity by PFOA. The carnitine palmitoyl-transferase I inhibitor 2-bromopalmitic acid produced a 2.5-fold increase in ACO stimulatory activity and reduced both ciprofibrate- and PFOA-mediated stimulations of ACO activity.

Cycloheximide treatment reduced PFOA- and ciprofibrate- induced ACO activities; however, the response to oleic acid was not blocked and increased slightly.

In rat and human PPARalpha transactivation assays, the rank order of activation was ciprofibrate > PFOA > oleic acid > or = octanoic acid > octanedioic acid or perfluorooctanol (inactive). PFOA, ciprofibrate and oleic acid were activators of rPPARalpha at concentrations that correlated favorably with the changes in ACO activity in cell culture. Octanoic acid did not increase ACO activity and was a weak activator of PPARalpha.

These findings suggest that fatty acids such as oleic acid (endogenous fatty acids) and PFOA (a stable fatty acid) act through more than one pathway to increase ACO activity in rat hepatocytes. We conclude that the potent effects of PFOA are primarily mediated by a mechanism that includes the activation of liver PPARalpha.

Test substance : PFOA
06.12.2005 (337)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : The purpose of this study was to test the hypothesis that a variety of structurally dissimilar peroxisomal proliferators inhibited O2 uptake and caused O2-dependent hepatotoxicity in the perfused rat liver. Aspirin, valproate, ethylhexanol, clofibric acid, ciprofibrate and perfluorooctanoate

were selected as a representative group of weak, moderate, and potent peroxisomal proliferators, respectively.

Result : All compounds studied inhibited state 3 but not state 4 rates of oxygen uptake in isolated mitochondria (perfluorooctanoate greater than ciprofibrate greater than ethylhexanol greater than clofibric acid greater than aspirin greater than valproate; half maximal inhibition occurred at concentrations ranging from 0.6 to 3.2 mM depending on the compound). Clofibric acid, ethylhexanol and aspirin inhibited oxygen uptake only in upstream, oxygen-rich periportal regions of the perfused liver lobule by 30-40%. Perfusion with the six agents studied caused release of lactate dehydrogenase into the effluent perfusate in a dose-dependent manner and caused damage predominantly in periportal regions of the lobule as reflected by trypan blue uptake. A strong correlation between the concentration of compound needed to inhibit respiration in isolated mitochondria and cause hepatotoxicity in the perfused liver was observed. It is proposed that peroxisomal proliferators accumulate in the liver due to their lipophilicity where they inhibit actively respiring mitochondria in periportal regions of the liver lobule and cause local toxicity.

Test substance : PFOA

06.12.2005 (366)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : In this study, seven structurally dissimilar peroxisome proliferating agents were shown to uncouple oxidative phosphorylation in isolated rat liver mitochondria.

Result : Perfluorooctanoate (0.5 mM) increased succinate-induced (state 4) mitochondrial respiration by over 50% while stimulation of state 3 respiration with ADP was minimal (i.e., uncoupling occurred). Interestingly, compounds which are potent carcinogens in vivo (e.g., Wy-14,643 and perfluorooctanoate) were more powerful uncouplers of oxidative phosphorylation in vitro than weak tumor-causing agents (e.g., valproate).

Test substance : PFOA

04.11.2005 (365)

Endpoint : other: Peroxisomal beta-oxidation
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male/female
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : The potency to accumulate triglyceride (TG) was compared between

perfluorinated fatty acids (PFCAs) with different carbon chain lengths in the liver of male and female rats and induction of peroxisomal beta-oxidation

Result : In male rats, either perfluoroheptanoic acid (C7) or PFOA (C8) had no effect, although perfluorononanoic acid (C9) and PFDA (C10) markedly accumulated TG. In female rats, C7, C8, and C9 did not cause TG accumulation, whereas C10 caused TG accumulation at the same level as in male rats. TG accumulation induced by C9 was regulated by the level of testosterone in male rats. In contrast with TG accumulation, peroxisomal beta-oxidation was induced by C8, C9, and C10 in male rats and by C9 and C10 in female rats. Only a slight difference was observed in the induction by C9 between male and female rats. The induction of TG accumulation by these PFCAs occurred in a dose-dependent manner and significantly correlated with hepatic concentrations of PFCA regardless of their carbon chain length, as was observed with induction of peroxisomal beta-oxidation There is, however, a striking difference in the hepatic concentration of PFCA required to cause induction of TG accumulation and that of peroxisomal beta-oxidation The concentration of PFCA required to induce TG accumulation is much higher than that to induce peroxisomal beta-oxidation. These results strongly suggest that TG accumulation induced by PFCAs, as well as the induction of peroxisomal beta-oxidation, is dependent only on the number of PFCA molecules in hepatocytes, but is not due to the difference in their chemical structures, and that there is a marked difference in the PFCA threshold to cause distinct biological effects.

Test substance : PFOA

06.12.2005 (391)

Endpoint : other: Peroxisomal proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : PFDA and PFOA belong to the structurally diverse group of compounds known to cause peroxisomal proliferation. It has been hypothesized that the common mode of action of these compounds is that they act through an activated coenzyme A (CoA) thioester. Using rat liver microsomal and isolated rat hepatocytes incubation conditions, it was determined if CoA conjugates could be produced.

Result : Using rat liver microsomal and isolated rat hepatocytes incubation conditions that were effective in producing a CoA conjugate of clofibric acid, no corresponding CoA derivative could be found for either PFDA or PFOA.

Test substance : PFOA

06.12.2005 (400)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :

No. of animals :
Method : other
Year : 1999
GLP : no data
Test substance : other TS

Method : The hypolipidemic effect is evoked by various peroxisome proliferators. Modulation of gene transcription via peroxisome proliferator-activated receptor (PPAR) is generally responsible for this effect. In addition, we have found a PPAR-independent mechanism in which fibrates, known peroxisome proliferators, decrease hepatic secretion of very low density lipoproteins (VLDL) through inhibition of phosphatidylcholine synthesis via methylation of phosphatidylethanolamine (PE). In the present study, we show a novel mechanism by which PFOA, a potent peroxisome proliferator and inhibitor of PE methylation, exerts its hypolipidemic effect.

Result : PFOA (100 microM) added to the medium rapidly decreased the secretion of triglyceride by cultured rat hepatocytes, which was independent of the activity of cellular PE methylation. Analysis of the density of apoB secreted into the medium showed that PFOA decreased apoB48 in VLDL, but increased apoB48 in the bottom d>1.21 fraction. This lipid-poor apoB48 was also generated by incubating medium that had been harvested from control cells with PFOA, indicating that PFOA has the ability to dissociate apoB48 from lipoprotein particles. Exposure of cells to PFOA for 2 h prior to the experiment was sufficient to generate lipid-poor apoB48, indicating that PFOA exerted its effect intracellularly. Taken together, the data suggest that a strong interaction of PFOA with apoB48 disturbs the association of apoB48 with lipids in the process of intracellular VLDL assembly, thereby inhibiting VLDL secretion. This study shows that the mechanisms of hypolipidemic effect caused by various classes of peroxisome proliferators are diverse.

Test substance : PFOA

06.12.2005 (465)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1994
GLP : no data
Test substance : other TS

Method : Morris hepatoma 7800C1 cells (from rat) were exposed to 500 mM PFOA in the culture medium for 7 days.

Result : Treatment resulted in inductions of catalase, lauroyl-CoA oxidase (which catalyzes the first step in peroxisomal beta-oxidation) and of cytochrome P-450IVA (specialized for omega- and omega-1 hydroxylation of fatty acids). Northern blot analysis revealed that the level of mRNA for peroxisomal fatty acyl-CoA oxidase was enhanced in cells treated with PFOA. Inductions of the enzymes mentioned above are generally connected with peroxisome proliferation in vivo. This work also includes a comparison between the activities of catalase, lauroyl-CoA oxidase, DT-diaphorase and glutathione transferase in rat liver homogenate and 7800C1 cells in order to investigate to what extent this cell line differs from the situation in vivo. The findings suggest that the cells selectively lost most of their peroxisomes during transformation into a cell line and subsequent propagation. The control activities of catalase and lauroyl-CoA oxidase

(marker enzymes for peroxisomes) were only about 2% of the corresponding enzyme activities in rat liver. In addition, a morphological study revealed that the frequency of peroxisomes in 7800C1 cells is very low. The control activity of glutathione transferase in 7800C1 cells was 11% of the corresponding activity in rat liver homogenate, whereas the level of DT-diaphorase was virtually the same in 7800C1 cells as in rat liver. Electron microscopic investigation of the control cultures revealed all signs of viable cells, with well-developed cell organelles. Treatment of 7800C1 cells with 500 mM PFOA has little effect on cellular morphology.

Test substance : PFOA

06.12.2005 (568)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1995
GLP : no data
Test substance : other TS

Method : Morris hepatoma 7800C1 cells (from rat) were exposed to 500 mM perfluorooctanoic acid (PFOA) in the culture medium for 7 days.

Result : Treatment of Morris hepatoma cells with the man-made peroxisome proliferator, PFOA, together with all-trans-retinoic acid did not result in any synergistic effect on this same enzyme activity demonstrating that peroxisome proliferation in Morris hepatoma cells by PFOA is not as dependent on the level of retinoic acid as is the same process caused by arachidonic acid.

Test substance : PFOA

06.12.2005 (573)

Endpoint : other: Peroxisome proliferators.
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male
Strain : Wistar
Route of admin. :
No. of animals :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : In order to investigate a proposed relationship between induction of hepatic microsomal lauric acid hydroxylase activity and peroxisome proliferation in the liver, male Wistar rats were treated with peroxisome proliferating compounds, and the lauric acid hydroxylase activity, the immunochemical detectable levels of cytochrome P450 4A1 and the activities of peroxisomal enzymes were determined. In addition, the levels of cytochrome P450 4A1 and lauric acid hydroxylase activities were studied after treatment of rats with three cytochrome P450 inducers.

Result : After treatment with aroclor-1254, phenobarbital or 3-methylcholanthrene total cytochrome P450 was 1.7-2.7 times induced. However, no induction of lauric acid omega-hydroxylase activities or P450 4A1 levels were found.

After treatment of rats with di(2-ethylhexyl)phthalate (DEHP) a dose-dependent induction of lauric acid omega-hydroxylase activities, levels of cytochrome P450 4A1 and peroxisomal fatty acid beta-oxidation was found. Even at a dose-level of 100 mg DEHP/kg body weight per day a significant induction of these activities was observed. The main metabolites of DEHP, mono(2-ethylhexyl)phthalate and 2-ethyl-1-hexanol, also caused an induction of levels of P450 4A1, lauric acid omega-hydroxylase activities and the activity of peroxisomal palmitoyl-CoA oxidase. 2-Ethyl-1-hexanoic acid did not influence lauric acid omega-hydroxylase activities, but did induce levels of P450 4A1 and palmitoyl-CoA oxidase activities. Three other compounds (PFOA, valproate and nafenopin) induced both lauric acid omega-hydroxylase activity and peroxisomal palmitoyl-CoA oxidase activity. The plasticizer, di(2-ethylhexyl)adipate, did not induce levels of P450 4A1, lauric acid omega-hydroxylase activities or palmitoyl-CoA oxidase activities. With the compounds tested a close association between the induction of lauric acid omega-hydroxylase activities and peroxisomal palmitoyl-CoA oxidase activity was found. These data support the theory that peroxisome proliferating compounds do induce lauric acid omega-hydroxylase activities and that there might be a mechanistic inter-relationship between peroxisome proliferation and induction of lauric acid omega-hydroxylase activities.

Test substance : PFOA

06.12.2005 (155)

Endpoint : other: Peroxisome proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1991
GLP : no data
Test substance : other TS

Method : The characteristics of peroxisome proliferation were determined in cultured rat hepatocytes.

Result : In primary cultured rat hepatocytes, 100 uM PFOA induced peroxisomal fatty acyl-CoA oxidase (FACO) with the same time-dependent pattern as xenobiotics such as ciprofibrate (CIPRO). The maximum FACO induction by PFOA was found after 72 hours. PFOA also produced time-dependent increases in laurate hydroxylase (LH) and carnitine acetyltransferase (CAT). CIPRO and PFOA gave ED50 values for maximal FACO induction of 4.0 and 25.3 uM, respectively. A low PFOA concentration (1 uM) shifted the dose-response curve of FACO induction by CIPRO to the right. With 100 uM PFOA, the inductive effects of CIPRO reached the same maximum response as that seen with PFOA (100 uM) or CIPRO (30 uM) alone. Octanoic acid (OA) [300 uM] did not modify PFOA (10 or 30 uM) induction of FACO whereas octanedioic acid (OD) [300 uM] slightly increased FACO induction by PFOA (30 uM). OD did not cause FACO induction. These results suggest that 1) PFOA like xenobiotics, may act through a common pathway leading to peroxisome proliferation, and 2) dicarboxylic FAs, unlike monocarboxylic FAs, act to enhance the peroxisome proliferation response.

Test substance : PFOA

06.12.2005 (335)

Endpoint : other: Peroxisome proliferation.
Study descr. in chapter :

Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1989
GLP : no data
Test substance : other TS

Method : Fatty acids are natural substrates for the peroxisomal beta-oxidation systems and may regulate the proliferation of this organelle. The effects of decanoic acid, octanoic acid, and butanoic acid, and the metabolically stable PFDA, PFOA, and perfluorobutanoic acid (PFBA) were examined in primary rat hepatocytes.
Result : Cells were incubated with each fatty acid and clofibrate (CPIB) (0.001 to 1.0 mM) for 72 hours, and the peroxisome proliferation (PP) associated activities of fatty acyl-CoA oxidase (FACO) and microsomal laurate hydroxylase (LH) measured. Only CPIB and PFBA were similarly active giving maximal responses of FACO and LH activities at 0.3 to 1.0 mM. By comparison, maximal inductive effects of PFDA and PFOA were observed at 0.03 to 0.1 mM with cytotoxicity seen at > 0.1 mM. These results show that stable perfluorinated FAs are potent inducers of PP in this cell system, and they should be useful tools to examine the role of FA on PP.
Test substance : PFOA
06.12.2005 (334)

Endpoint : other: Microsomal peroxidation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1981
GLP : no data
Test substance : other TS

Method : The ability was determined for PFOA to solubilize microsomes at surfactant concentrations that either stimulated peroxidation or potentiated iron-induced peroxidation. Ascorbic acid was the reducing agent; PFOA concentrations were 0.3 to 0.5 uM; Tween 20 (a surfactant) concentrations were 0.02 to 0.5 uM; and the malondialdehyde (MDA) control was 3 nmol/mg protein/35 minutes without added iron or 32 nmol/mg protein/35 minutes with 1 uM of Fe+2.
Result : Both PFOA and Tween 20 solubilized microsomes at surfactant concentrations that either stimulated peroxidation or potentiated iron-induced peroxidation.
Test substance : PFOA
04.11.2005 (534)

Endpoint : other: Microsomal lipid peroxidation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :

Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1980
GLP : no data
Test substance : other TS

Method : PFOA was tested for its ability to stimulate rat liver microsomal lipid peroxidation (LP). LP stimulation was compared to that by CCl4 using NADPH or ascorbic acid as a reducing agent.

Result : Using NADPH, 1.5 mM PFOA or 4.9 mM CCl4 (2.5 uL CCl4/mg protein) caused a 4-fold increase in malondialdehyde (MDA) formation (control rate = 0.42 (n = 15) nmoles MDA/min/mg protein). Half maximal effects occurred at 0.8 mM PFOA or 0.5 mM CCl4. Increasing PFOA to 3 mM or more sharply abolished MDA formation, yet 20 mM CCl4 still produced 80% maximal stimulation. Using NADPH, 0.01 to 1.0 mM EDTA inhibited 100% of PFOA stimulation but only 67% of the CCl4 stimulation. The EDTA data suggested iron contamination of PFOA, but atomic absorption analysis indicated less than 15 nM iron in the PFOA sample. Using ascorbic acid, 1.5 mM PFOA had similar MDA stimulatory effects as 5 uM Fe+2. Microsomes incubated with 1.5 mM PFOA, 1 uM Fe+2, and ascorbic acid yielded more MDA than microsomes incubated with 10 uM Fe+2 and ascorbic acid. Under similar conditions, CCl4 addition had no effect. These data suggest that while PFOA stimulates LP, such stimulation is different than that by CCl4.

Test substance : PFOA

16.11.2005 (532) (533)

Endpoint : other: Peroxisomal proliferation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year :
GLP : no data
Test substance : other TS

Method : PFOA is known to cause peroxisome proliferation. Several studies make use of this known quality and have used PFOA as a positive control when investigating other chemicals for their ability to cause peroxisome proliferation. These studies are listed here.

Test substance : PFOA

08.11.2005 (356) (377) (383) (384) (401) (426) (436) (455)

Endpoint : other: Peroxisomal enzymes
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1990
GLP : no data

Test substance : other TS

Method : Peroxisomal enzymes were measured in intact and adrenalectomized rats orally administered 150 mg/kg of PFOA.

Result : In intact rats, an oral administration of 150 mg/kg of PFOA caused a 40% increase in liver/body weight ratios within 48 hours. While the increase in adrenalectomized rats was only 28%, corticosterone supplementation restored hepatomegaly in these rats to levels observed in the intact rats. When calculated per gram of liver weight, the cyanide-insensitive oxidation of palmitoyl CoA was 6.5 and 10.45 umole NAD+ reduced/min in intact and adrenalectomized rats, respectively. Corticosterone supplements to adrenalectomized-treated rats restored peroxisomal beta-oxidation values comparable to those obtained in intact rats. However, when the magnitude of liver enlargement was considered, there was no significant differences in peroxisomal beta-oxidative capacities among these groups of rats. Similar results were obtained for catalase, another peroxisomal marker enzyme. Taken collectively, these data show that apparent differences in peroxisomal enzyme activities per gram of liver observed in intact and adrenalectomized rats are solely due to dissimilar increases in liver weights produced in these animals, and not due to regulation of these enzymes by adrenal hormones.

Test substance : PFOA

04.11.2005 (596)

Endpoint : other: Peroxisome proliferation

Study descr. in chapter :

Reference :

Type :

Species :

Sex :

Strain :

Route of admin. :

No. of animals :

Method : other

Year : 2002

GLP : no data

Test substance : other TS

Method : This paper reports the development of new methods for mathematical characterization of effects of different toxic agents on the cellular proteome. It describes numerical characterization of proteomics maps based on mathematical invariants. A graph is first associated with a proteomics map by considering partial ordering of spots on 2-D gels by ordering proteins with respect to the mass and the charge, the two properties by which proteins are separated. The graph is then embedded over the map, and several graph theoretical invariants have been constructed. In particular it considers invariants that can be extracted from the Euclidean distance-adjacency matrix of the embedded graph, in which only Euclidean distances between adjacent vertices of a graph are considered. The approach is illustrated using proteomics patterns of normal liver cells of rats and those derived from liver cells of animals exposed to four peroxisome proliferators. In contrast to direct comparison of spot abundance this approach incorporates information on spots locations. The difference between the two approaches is that in the first case only changes in abundances are considered as a measure of perturbation of the proteome map, but in the second case not only the charge but also the mass of proteins are used for ordering protein spots.

Test substance : PFOA

06.12.2005 (505)

Endpoint : Immunotoxicity

Study descr. in chapter :

Reference	:	
Type	:	
Species	:	mouse
Sex	:	male
Strain	:	C57BL
Route of admin.	:	oral feed
No. of animals	:	
Vehicle	:	
Exposure period	:	10 day(s)
Frequency of treatm.	:	Daily
Doses	:	0.001%-0.05% PFOA (w/w)
Control group	:	yes
Observation period	:	
Result	:	
Method	:	other
Year	:	2001
GLP	:	no data
Test substance	:	other TS

Method : Male C57B1/6 mice weighing 24-28 g (about 8-10 weeks old) were housed and treated in steel cages in groups of four. These animals were maintained on a 12-hr light/dark cycle at 25°C and given free access to laboratory chow R3 containing 5% fat, 24% protein, and 49% carbohydrate (Astra Ewos AB). PFOA was dissolved in 20 mL acetone and mixed with 500 g powdered food to prepare a diet containing 0.001% to 0.05% PFOA (w/w). This chow was dried in a ventilated hood until no smell of acetone was detectable. Because mice scatter powdered food, both the normal and PFOA-containing chows were prepared in the form of pellets to allow determination of food intake. The mice were also weighed each day. For investigation of the dose dependency of the effects of PFOA on these lymphoid organs, mice received diets containing 0.001-0.05% PFOA (w/w) for 10 days. For examination of the time-course, a diet containing 0.02% PFOA was administered for 2-10 days. To monitor recovery, the animals were fed a diet containing 0.02% PFOA (w/w) for 7 days, after which they were given normal diet for 2-10 days.

At the end of the feeding period, the mice were killed by ether inhalation to avoid coagulation of the blood. The liver, thymus, and spleen were dissected out and weighed. The liver samples were then homogenized and subfractionated.

Result : Comparison of the dose-dependencies and time-courses indicated that the peroxisome proliferative effect occurred prior to atrophy of both the thymus and spleen. However, following withdrawal of PFOA from the diet, the weight of the thymus and spleen rapidly returned to normal within 10 and 5 days, respectively, in contrast to the more persistent peroxisome proliferation. Furthermore, the changes in thymus and spleen weight upon PFOA treatment and the following withdrawal from diet paralleled the changes in total thymocyte and splenocyte counts, respectively It was found previously that the decreases in the thymocyte populations present in the S and G2/M phases, as well as in the number of CD4+CD8+ cells upon PFOA treatment, were the most dramatic, perhaps reflecting inhibition of thymocyte proliferation in connection with thymocyte development. Here, the recovery of thymocytes began with increases in the populations in these same phases of the cell cycle, with CD4+CD8+ cells recovering most rapidly, lending further support to the previous hypothesis.

06.12.2005 (645)

Endpoint	:	Immunotoxicity
Study descr. in chapter	:	
Reference	:	
Type	:	

Species : mouse
Sex : male
Strain : C57BL
Route of admin. : oral feed
No. of animals :
Method : other
Year : 2000
GLP : no data
Test substance : other TS

Method : The effects of peroxisome proliferators on the immune system of male C57B1/6 mice have been investigated.

Result : Significant atrophy of the thymus and spleen was observed in animals treated with potent peroxisome proliferators (e.g. PFOA, di(2-ethylhexyl)phthalate (DEHP), Wy-14643 and nafenopin), whereas the effects of a moderate peroxisome proliferator (i.e. acetylsalicylic acid (ASA)) were relatively weak. The time course of thymic and splenic atrophy caused by PFOA was found to resemble the time course of the increase in liver weight and of peroxisome proliferation. Analysis of the numbers and phenotypes of thymocytes and splenocytes from PFOA-treated mice revealed the following: (i) the numbers of thymocytes and splenocytes were decreased > 90% and about 50%, respectively, by PFOA treatment; (ii) although all populations of thymocytes were decreased, the immature CD4+CD8+ population was decreased most dramatically; (iii) the numbers of both T and B cells in the spleen were decreased by PFOA treatment. Analysis of the cell cycle of thymocytes indicated that the thymic atrophy caused by PFOA in mice results, at least in part, from inhibition of thymocyte proliferation. Interestingly, in vitro exposure to PFOA for up to 24 hours did not produce analogous effects in either thymocytes or splenocytes. Thus, the thymic and splenic atrophy caused by PFOA appears to involve an indirect pathway.

Test substance : PFOA

06.12.2005 (644)

Endpoint : Immunotoxicity
Study descr. in chapter :
Reference :
Type :
Species : mouse
Sex : male
Strain : C57BL
Route of admin. : oral feed
No. of animals :
Vehicle :
Exposure period :
Frequency of treatm. :
Doses : 0.02%
Control group : yes
Observation period :
Result :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : The effects of the potent PP PFOA on the adaptive immunity of mice was evaluated both in vivo and ex vivo. The in vivo immune response examined involved immunization of mice with horse red blood cells (HRBCs), displaying T-cell-dependent antigens after pretreatment with a PFOA-containing diet for 10 days. Subsequent quantitation of the primary humoral response was performed employing both the plaque-forming cell (PFC) assay and determination of the antibody titer by ELISA.

Result : The results demonstrate that oral administration of PFOA prevents both the increases in plaque formations by anti-IgM and -IgG and in serum levels of IgM and IgG normally evoked by such immunization. Ex vivo spleen cells proliferation (assayed as incorporation of 3H-thymidine) in response to both T- and B-cell activators was attenuated by dietary treatment with PFOA, although the analogous in vitro treatment of mouse spleen cells with this same compound had no such effects. Thus, the relatively metabolically inert PP PFOA may exert adaptive immunosuppression in mice by an indirect mechanism.

Test substance : PFOA

06.12.2005 (642)

Endpoint : Immunotoxicity
Study descr. in chapter :
Reference :
Type :
Species : mouse
Sex : male
Strain : C57BL
Route of admin. : oral feed
No. of animals :
Vehicle :
Exposure period : 7 day(s)
Frequency of treatm. : Daily
Doses : 0.02%
Control group : yes
Observation period :
Result :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : Since the peroxisome proliferator-activated receptor alpha (PPARalpha) plays a central role in mediating the pleiotropic responses exerted by PPs, we have compared here the immunomodulating effects of the PPs PFOA (0.02% in the diet for 7 days) and Wy-14,643 (0.125% in the diet for 7 days) in wild-type and PPARalpha-null mice.

Result : The reductions in spleen weight and in the number of splenocytes caused by PP treatment in wild-type mice was not observed in PPARalpha-null mice. Furthermore, the reductions in thymus weight and in the number of thymocytes were potently attenuated in the latter animals. Similarly, the decreases in the size of the CD4(+)CD8(+) population of cells in the thymus and in the number of thymocytes in the S and G2/M phases of the cell cycle observed in wild-type mice administered PPs were much less extensive in PPARalpha-null mice. Finally, in contrast to the case of wild-type animals, the response of splenocytes isolated from the spleen of PP-treated PPARalpha-null mice to appropriate T- or B-cell activators in vitro was not reduced. Altogether, these data indicate that PPARalpha plays a major role in the immunomodulation caused by PPs.

Test substance : PFOA

06.12.2005 (643)

Endpoint : Immunotoxicity
Study descr. in chapter :
Reference :
Type :
Species : mouse
Sex :
Strain : Balb/c
Route of admin. : dermal
No. of animals :

Vehicle :
Exposure period :
Frequency of treatm. :
Doses : 0.01-2.0% (0.25-50 mg/kg)
Control group :
Observation period :
Result :
Method : other
Year : 2005
GLP : no data
Test substance : other TS

Method : Studies were conducted to investigate the role of dermal exposure to PFOA on the hypersensitivity response to ovalbumin in a murine model. BALB/c mice were dermally exposed to concentrations of PFOA ranging from 0.01 to 2.0% (0.25 to 50 mg/kg) for 4 days. In hypersensitivity studies, mice were also intraperitoneally injected with 7.5 ug ovalbumin and 2 mg alum on days 1 and 10 and in some studies, intratracheally challenged with 250 ug ovalbumin on days 17 and 26. Endpoints for studies included body and organ weights and cellularities, IgE, airway hyperactivity, and lung histopathology.

Result : Following exposure to PFOA, an increase in liver weights and a decrease in thymus and spleen weights and cellularities were observed. Similar immunomodulatory trends were demonstrated in mice co-administered PFOA and ovalbumin. Greater than a 2-fold increase in total IgE was demonstrated when mice were co-exposed with concentrations of PFOA ranging from 0.75 to 1.5%, while the ovalbumin-specific IgE response peaked after a 3-fold increase in 0.75% PFOA co-exposed animals as compared to the ovalbumin alone exposed animals. Antigen-specific airway hyperreactivity was increased in the 1.0% PFOA co-exposed group, with a dose-responsive pleiotropic cell response characterized by eosinophilia and mucin production, in animals co-exposed to concentrations of PFOA up to 1.0%, as compared to ovalbumin alone exposed animals. PFOA was demonstrated to be immunotoxic in a murine model following dermal exposure, with an enhancement of the hypersensitivity response to ovalbumin suggesting that PFOA exposure may augment the IgE response to environmental allergens.

Test substance : PFOA

06.12.2005 (259)

Endpoint : Hematoxicity
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2004
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The objective of this study was to evaluate whether or not the in vitro addition of APFO (branched and linear), APFO (linear only), or APFO (branched only) to pooled normal fasted rat serum interfered with the determination of any of the following clinical pathology parameters: triglycerides, total cholesterol, high-density lipoprotein cholesterol, or non-high-density lipoprotein cholesterol. The test substance was added to fresh phosphate buffered saline (PBS) or pooled normal rat serum. Subsequently, serial dilutions were performed. Dilutions in PBS and serum,

and negative controls of PBS and serum, were analyzed for triglyceride, total cholesterol, HDL cholesterol, and non-HDL cholesterol.

Result : Neither APFO (branched and linear), APFO (linear only), nor APFO (branched only), at concentrations up to 720 ug/mL, interfered with the determination of concentration of triglycerides, total cholesterol, HDL cholesterol, or non-HDL cholesterol in phosphate-buffered saline or in pooled normal rat serum.

08.11.2005 (232)

Endpoint : other: Effect on mRNA levels in liver
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : oral feed
No. of animals :
Vehicle :
Exposure period : 10 day(s)
Frequency of treatm. : Daily
Doses : 0.05%
Control group : yes, concurrent no treatment
Observation period :
Result :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : The question as to whether peroxisome proliferators increase mitochondrial biogenesis is addressed by examining the influence of clofibrate, PFOA, and acetylsalicylic acid on the mRNA levels for certain mitochondrial inner-membrane proteins. Male Sprague-Dawley rats were administered a diet containing 0.05% PFOA for 10 days.

Result : Clofibrate, perfluorooctanoic acid, and acetylsalicylic acid all increased the mRNA levels for the mitochondrial-encoded respiratory-chain components cytochrome c oxidase subunit I and NADH dehydrogenase subunit I. Mitochondrial 16S rRNA was also induced by clofibrate. The mRNA levels for the nuclear-encoded mitochondrial inner-membrane proteins adenine nucleotide translocator and cytochrome c1 were selectively induced by the different peroxisome proliferators. Malic enzyme, which is induced by thyroid hormone, was also induced by the three peroxisome proliferators tested. These effects are in some ways similar to those obtained with thyroid hormone.

Test substance : PFOA

06.12.2005 (113)

Endpoint : other: Effect on liver-fatty acid binding protein
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : Liver-fatty acid binding protein (L-FABP) is an abundant intracellular lipid-carrier protein. The hypothesis that perfluorooctanesulfonate (PFOS), PFOA, and certain related perfluorooctanesulfonamide-based fluorochemicals (PFOSAs) can interfere with the binding affinity of L-FABP for fatty acids was tested.

Result : The relative effectiveness of PFOA, PFOS, N-ethylperfluorooctanesulfonamide (N-EtFOSA), N-ethylperfluorooctanesulfonamido ethanol (N-EtFOSE), and of the strong peroxisome proliferator Wyeth-14643 (WY) to inhibit 11-(5-dimethylaminonapthalenesulphonyl)undecanoic acid (DAUDA) binding to L-FABP was determined. The dissociation constant (Kd) of the DAUDA-L-FABP complex was 0.47 nM. PFOS exhibited the highest level of inhibition of DAUDA-L-FABP binding in the competitive binding assays, followed by N-EtFOSA, WY, and, with equal IC(50)s, N-EtFOSE and PFOA. The in vitro data presented in this study support the hypothesis that these fluorochemicals may interfere with the binding of fatty acids or other endogenous ligands to L-FABP. Furthermore, this work provides evidence to support the hypothesis that displacement of endogenous ligands from L-FABP may contribute to toxicity in rodents fed these fluorochemicals.

Test substance : PFOA

06.12.2005 (424)

Endpoint : other: Binding in rat liver
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex : male
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2001
GLP : no data
Test substance : other TS

Method : Subcellular fractionation was determined in the liver tissue from 14C-PFOA-dosed rats.

Result : Subcellular fractionation of the liver tissue from 14C-PFOA-dosed rats exhibited nearly equal dose distribution in nuclei (41%) and cytosol (42%) fractions. However, the 14C-PFOA preferentially distributed in the nuclei of male rat liver (54% versus 25% in the cytosol) suggesting that a gender specific PFOA binding site may be prevalent in the nuclei of male rat liver. Also observed using Western blot analysis was binding of 14C-PFOA to rat albumin, a high molecular weight protein (~ 150 kDa), and a low molecular weight protein (~ 14 kDa) in the sub-cellular nuclei fraction of rat liver, and several proteins ranging from 60 to 14 kDa in the cytosol fraction of rat liver.

Test substance : PFOA

04.11.2005 (563)

Endpoint : other: Binding with serum proteins
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2003

GLP : no data
Test substance : other TS

Method : The PFOS and PFOA binding to serum proteins was investigated by assessing its ability to displace a variety of steroid hormones from specific binding proteins in the serum of birds and fishes.
Result : Perfluorooctane sulfonic acid had only a weak ability to displace estrogen or testosterone from carp serum steroid binding proteins. Displacement of cortisone in avian sera occurred at relatively low PFOS concentrations. Corticosterone displacement potency increased with chain length, and sulfonic acids were more potent than carboxylic acids. The PFOS estimated EC10 concentration to cause these effects was 320 mM or greater, equivalent to serum concentrations greater than 160 mg/L. The estimated EC10 for PFOA was about 2-fold greater (652 uM) than that of PFOS. The potency of PFOA was consequently less than that of PFOS but still in the same order of magnitude. Using mass spectrometry and direct in vitro binding assays, PFOS was demonstrated to bind strongly to bovine serum albumin (BSA) in a 1:1 stoichiometric ratio. It appears that PFOS in serum is in general bound to albumins. Concentrations of PFOS required to saturate albumin would be in excess of 50 to 100 mg/L. Based on current environmental concentrations, it is unlikely that PFOS would cause displacement of hormones from serum proteins in wildlife.
Test substance : PFOA
08.11.2005 (343)

Endpoint : other: Binding ability of a human B-lymphoblastoid cell line
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1987
GLP : no data
Test substance : other TS

Method : The effect of the perfluorinated fatty acids PFOA and nonadecafluoro-n-decanoic acid (NDFDA) on the ability of a human B-lymphoblastoid cell line to bind the lipid-binding, membrane-impermeant, fluorescent dye merocyanine 540 (MC540) was studied.
Result : Subtoxic concentrations of perfluorinated fatty acids (0.9 mM PFOA; 0.5 mM NDFDA) greatly diminish binding of MC540 by normal plasma membranes, as determined by fluorescence flow cytometry. When perfluorinated fatty acids are added to cells at toxic or lethal concentrations (1.2 mM PFOA; 0.75 mM NDFDA), MC540 binding increases dramatically, with entrance of dye to internal membrane domains. Neither perfluorinated fatty acid molecule reduces the ability of surface immunoglobulin to migrate laterally and cap on cells. This suggests that perfluorinated fatty acids either interact directly with lipid binding sites for MC540, and thereby inhibit dye intercalation, or alter membrane lipid architecture and lipid packing to diminish MC540 binding. Both possibilities support a direct, physical, membrane-altering mechanism for perfluorinated fatty acid toxicity on mammalian cells.
Test substance : PFOA
06.12.2005 (410)

Endpoint : other: Protein binding study in rats
Study descr. in chapter :
Reference :

Type :
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : i.p.
No. of animals :
Method : other
Year : 1992
GLP : no data
Test substance : other TS

Method : PFDA and PFOA were examined to determine if they covalently bind cellular proteins in rats.
Result : The liver, plasma and testes of male rats treated with [1-14C] PFDA or PFOA (9.4 umol/kg) contained detectable levels of covalently bound 14C (0.1-0.5% of the tissue 14C content). Characterization of PFDA covalent binding to albumin in vitro showed that cysteine significantly decreased binding with no effect of methionine, suggesting protein sulfhydryl groups are involved. In cytosolic and microsomal incubation there was no effect of the addition of CoA, ATP or NADPH on the magnitude of the covalent binding of PFDA. Therefore PFDA need not be metabolically activated to form covalent adducts. Despite demonstration of covalent binding of PFDA and PFOA to proteins both in vivo and in vitro, the role of this macromolecular binding in perfluorinated fatty acid toxicity is not known.
Test substance : PFOA
06.12.2005 (500) (612)

Endpoint : other: Protein binding in human, rat, and monkey plasma.
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2003
GLP : no
Test substance : other TS

Method : The objective of this study was to determine the percent of protein binding in human, rat, and monkey plasma as well as various human-derived plasma protein fractions.
Result : Protein binding of 3 fluorinated compounds perfluorohexane sulfonate [PFHS], perfluorooctanoate sulfonate [PFOS], and PFOA was evaluated in seven separate human-derived plasma protein fractions [albumin, gamma-globulin, alpha-globulin, fibrinogen, alpha-2-macroglobulin, transferrin, and beta-lipoproteins] at two different protein fraction concentrations. Additionally, protein binding was evaluated in rat, human, and monkey plasma at 5 different concentrations. Albumin is by far the largest single protein binder for 2 of the 3 compounds tested at both concentrations. The third compound, PFOS, was found to be highly bound by both albumin and beta-lipoproteins. The protein binding experiments for the rat, human, and monkey plasma show very high levels of binding at all concentrations tested and no evidence of saturation.
Test substance : PFOA
06.12.2005 (575)

Endpoint : other: Coagulation of crystalline bovine albumin
Study descr. in chapter :
Reference :

Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1955
GLP : no data
Test substance : other TS

Method : Studies were conducted to determine the role of PFOA in preventing coagulation of crystalline bovine albumin.
Result : PFOA appeared to act on the hydrogen bond network of the protein, altering its immunochemical reactions. PFOA causes bovine serum albumin to form high molecular weight aggregates, the sizes of which depend on pH, ionic strength, type of buffer, protein, and acid concentrations.
Test substance : PFOA
04.11.2005 (246) (381)

Endpoint : other: Immunological properties of bovine serum albumin-PFOA complexes.
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1956
GLP : no
Test substance : other TS

Method : An investigation was undertaken of the physical-chemical and immunological properties of bovine serum albumin (BSA)-PFOA complexes heated under controlled conditions.
Result : Heated BSA and PFOA form complexes of micellar nature. Exhaustive dialysis at pH 5.2 precipitated the heat-denatured protein. Immunochemical studies with BSA-PFOA complexes corroborated the physical-chemical findings that PFOA does not protect BSA from heat denaturation. From viscosity and partial specific volume studies alone, no deduction can be made concerning the interaction of unheated BSA-PFOA complexes.
Test substance : PFOA
06.12.2005 (247)

Endpoint : other: Effect on mammalian B cell lines
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1987
GLP : no data
Test substance : other TS

Method : The toxicity of two perfluorinated fatty acids, PFOA and nonadecafluoro-n-decanoic acid (NDFDA), on three mammalian B cell lines was evaluated. Cells were exposed to the perfluorinated molecules for either 24 or 48 hours under a variety of culture conditions.

Result : Immunoglobulin secretion and surface membrane expression were unaffected by both PFOA and NDFDA at sublethal concentrations. Lethal effects of PFOA and NDFDA are diminished by either lowering culture temperature (37 to 20°C) or including fetal bovine serum or human serum albumin in media. At lethal concentrations, both PFOA and NDFDA possess detergent activity since they can release IgM in soluble form from a cell line that does not secrete immunoglobulins, and brief exposure (15 minutes) to 1-2 mM of both perfluorinated fatty acids results in solubilization of F4 cells equivalent to the anionic detergent deoxycholic acid. This suggests that at subtoxic concentrations, neither PFOA nor NDFDA alters expression or secretion of a differentiated gene product (IgM). At lethal levels, both chemicals cause increased solubilization of proteins from lymphoblastoid cell lines.

Test substance : PFOA

06.12.2005 (409) (411)

Endpoint : other: Toxicity of PFOA in L5178Y mouse lymphoma cells

Study descr. in chapter :

Reference :

Type :

Species :

Sex :

Strain :

Route of admin. :

No. of animals :

Method : other

Year : 1983

GLP : no data

Test substance : other TS

Method : The toxicity of PFOA was studied in vitro in L5178Y mouse lymphoma cells.

Result : PFOA did not impair clone-forming ability at any concentration; and neither did other straight-chain hydrogenated fatty acid analogs. All polyfluorinated acids tested (either perfluorinated or omega-hydro-analogs) with chain length 9 or greater caused impairment of clone-forming ability.

Test substance : PFOA

08.11.2005 (75)

Endpoint : other: Inhibitory effect on mycoplasma

Study descr. in chapter :

Reference :

Type :

Species :

Sex :

Strain :

Route of admin. :

No. of animals :

Method : other

Year : 1985

GLP : no data

Test substance : other TS

Method : A model system is described for elucidating the mechanisms of action of membrane-active toxic chemicals. Cell wall-less prokaryotes called mycoplasmas were used. Acholeplasma laidlawii is the sentinel organism for this study. Temperature, medium composition and genetic factors all

interact to create the final A. laidlawii cell membrane.

Result : Two commercially available perfluorinated acids, nonadecafluoro-n-decanoic acid (NDFDA) and PFOA were tested for inhibitory action on A. laidlawii JA1 cultures. The JA1 growth on agar was inhibited as detected by zones of inhibition around sterile filter paper disks previously loaded with 0.1 uM solution of each compound. When incubation was at 35°C or 25°C, inhibition zones were smaller when JA1 was grown in a high-cholesterol- rather than on a low-cholesterol-containing medium. Under low- or high-cholesterol supplementation, JA1 was more sensitive to NDFDA than to PFOA at 35°C. At 25°C incubation temperature, differences were less pronounced. Apparently, sensitivity to NDFDA and PFOA is related to membrane fluidity and each potentially has a different membrane level target.

Test substance : PFOA

06.12.2005 (416)

Endpoint : other: Growth of mycoplasma
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1986
GLP : no data
Test substance : other TS

Method : A prokaryotic cell system was developed that can be used to determine the toxic action of chemicals acting at the level of the eukaryotic or prokaryotic cytoplasmic membrane. Cell wall-less microbes known as mycoplasmas are used.

Result : PFOA and PFDA inhibited the growth of the test mycoplasmas. Two apparent activities were observed. At high concentrations, (>10 mM), a detergent-like action was noted. At low concentrations, (<10 mM), cell death was observed without detectable cell lysis. Altering the cell membrane (the presumed target of the toxic compounds) resulted in altered levels of toxicity.

Test substance : PFOA

06.12.2005 (415)

Endpoint : other: Mitochondrial bioenergetics disruption
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2003
GLP : no data
Test substance : other TS

Method : PFOA, perfluorooctanesulfonate (PFOS), and substituted perfluorooctanesulfonamides disrupt mitochondrial bioenergetics in one of three ways: by stimulating proton conductance to uncouple mitochondrial respiration, as inducers of the mitochondrial permeability transition (MPT), or by causing the nonspecific increase in ion permeability across the

mitochondrial membranes. The purpose of this investigation was to screen several members of this class of compounds, PFOA, PFOS, perfluorooctanesulfonamide (FOSA), perfluorooctanesulfonamidoacetate (FOSAA),
N-ethylperfluorooctanesulfonamide (N-Et-FOSA), 2-(N-ethylperfluorooctanesulfonamido)ethyl alcohol (N-Et-FOSE), and N-ethylperfluorooctanesulfonamido acetate (N-Et-FOSAA) to reveal a common structural characteristic responsible for induction of the mitochondrial permeability transition. Each compound was added at concentrations previously shown to alter mitochondrial respiration to a reaction medium containing glutamate/malate energized rat liver mitochondria. Mitochondrial swelling was monitored spectrophotometrically.

Result : PFOS, FOSA, N-Et-FOSA and N-Et-FOSE did not induce swelling at any concentration. In contrast, the carboxylated compounds PFOA, FOSAA, and N-ET-FOSAA induced calcium-dependent, cyclosporin A inhibited mitochondrial swelling. The fully substituted amide N-Et-FOSAA is the most potent inducer of the MPT, followed by FOSAA, then PFOA. The results indicate that the primary determinant of induction of the MPT is the carboxylic group, and that it is the induction of the MPT that is responsible for the observed interference with mitochondrial respiration by these carboxylated fluorochemicals. In a subsequent study, the role of MPT in the mechanism of toxicity associated with perfluorinated carboxylic acids was more thoroughly characterized. FOSSA and N-Et-FOSAA induced calcium-dependent mitochondrial swelling, inhibited uncoupled respiration, and induced ROS generation, all of which were inhibited by cyclosporin-A. Adding exogenous cytochrome c also restored uncoupled respiration. PFOA induced the MPT, however ROS generation was not detectable at the concentration tested. The non-carboxylated compounds PFOS, FOSA, N-Et-FOSA and N-Et-FOSE did not induce the MPT or ROS generation, nor did they inhibit uncoupled respiration.

Test substance : PFOA

06.12.2005 (456) (457)

Endpoint : other: Mitochondrial uncoupling
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2002
GLP : no data
Test substance : other TS

Method : This investigation characterize the structural determinants responsible for the mitochondrial uncoupling effect of several structurally related fluorochemicals. Included in the study were PFOA, PFOS, FOSA, the N-acetate of FOSA (perfluorooctanesulfonamido acetate, FOSAA), N-ethylperfluorooctanesulfonamide (N-EtFOSA), and the N-Et alcohol [2-(N-ethylperfluorooctanesulfonamido)ethyl alcohol, N-EtFOSE] and N-acetic acid (N-ethylperfluorooctanesulfonamidoacetate, N-Et-FOSAA) of N-EtFOSA. Each test compound was dissolved in ethanol and added directly to an incubation medium containing substrate-energized rat liver mitochondria. Mitochondrial respiration and membrane potential were measured concurrently using an oxygen electrode and a TPP+-selective electrode, respectively.

Result : All of the compounds. tested, at sufficiently high concentrations, had the capacity to interfere with mitochondrial respiration, albeit via different

mechanisms and with varying potencies. At sufficiently high concentrations, the free acids PFOA and PFOS caused a slight increase in the intrinsic proton leak of the mitochondrial inner membrane, which resembled a surfactant-like change in membrane fluidity. Similar effects were observed with the sulfonamide N-EtFOSE. Another fully substituted sulfonamide, N-EtFOSAA, at high concentrations caused inhibition of respiration, the release of cytochrome c, and high-amplitude swelling of mitochondria. The swelling was prevented by cyclosporin A or by EGTA, indicating that this compound induced the mitochondrial permeability transition. The unsubstituted and mono-substituted amides FOSA, N-EtFOSA, and FOSAA all exerted a strong uncoupling effect on mitochondria resembling that of protonophoric uncouplers. Among these compounds, FOSA was a very potent uncoupler of oxidative phosphorylation, with an IC50 of approx. 1 M. These data suggest that the protonated nitrogen atom with a favorable pKa is essential for the uncoupling action of perfluorooctane sulfonamides in mitochondria, which may be critical to the mechanism by which these compounds interfere with mitochondrial metabolism to induce peroxisome proliferation in vivo.

Test substance : PFOA

08.11.2005 (578) (579)

Endpoint : other: Mitochondrial activity of long-chain acyl-CoA synthetase

Study descr. in chapter :

Reference :

Type :

Species :

Sex :

Strain :

Route of admin. :

No. of animals :

Method : other

Year : 1991

GLP : no data

Test substance : other TS

Method : The effects were examined of PFDA and other perfluorinated carboxylic acids on ability to inhibit mitochondrial activity of long-chain acyl-CoA synthetase (ACS) in isolated rat hepatocyte suspensions and in rat liver mitochondria and microsomes.

Result : PFDA inhibited the oxidation of palmitic acid but not octanoic or pyruvic acids when hepatocytes were incubated with 1 mM PFDA. At this PFDA concentration the esterification of palmitic acid into triacylglycerols was also reduced. The activity of long-chain acyl-CoA synthetase (ACS), an enzyme essential for both oxidation and esterification of fatty acids, was reduced in hepatocytes incubated with 1 mM PFDA. Carnitine palmitoyltransferase (CPT), an important enzyme for the oxidation of long-chain fatty acids, was not altered in hepatocytes incubated with this PFDA concentration. In rat liver mitochondria, palmitate oxidation and ACS activity were reduced significantly (P less than 0.01) at a PFDA concentration that had no effect on CPT activity. The inhibition of ACS by PFDA was similar in liver mitochondria and microsome preparations. In mitochondria incubated with PFDA, the inhibition of ACS appears to be noncompetitive for the substrates palmitic acid and CoA. However, the ACS inhibition by PFDA appeared to be competitive for the ATP binding site of the enzyme. Several chain length perfluorinated fatty acids were examined for their ability to inhibit mitochondrial ACS. Short-chain perfluorinated fatty acids (perfluoropropionic and perfluorobutyric acid) did not inhibit ACS activity. However, medium-chain perfluorinated acids (perfluorooctanoic, perfluorononanoic and perfluorodecanoic acid) were found to be potent inhibitors of ACS in isolated mitochondria. Whether ACS inhibition is causally related to PFDA-induced peroxisome proliferation and altered lipid metabolism seen in vivo is yet to be determined.

Test substance : PFOA
16.11.2005 (613)

Endpoint : other: Mitochondrial activity of long-chain acyl-CoA synthetase
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1993
GLP : no data
Test substance : other TS

Method : This experiment tested the hypothesis that peroxisome proliferators induce acyl-CoA binding protein (ACBP) in rat hepatocytes.
Result : The effects of two structurally dissimilar peroxisome proliferators perfluorodecanoic acid (PFDA) and clofibric acid (CPIB) were examined in primary rat hepatocyte cultures in a chemically defined media. Both compounds alter lipid metabolism in primary rat hepatocytes in a similar fashion, although PFDA is more potent than CPIB at inducing peroxisomal beta-oxidation. In addition, PFDA and CPIB compete with long-chain fatty acids for binding to FABP but do not compete with long-chain acyl-CoA esters for binding to ACBP. The concentration of ACBP and FABP was increased in peroxisome proliferator-treated hepatocytes relative to vehicle controls within 48 hours of treatment. Evidence is given to support increases in ACBP and FABP mRNA being the cause of the increased protein levels by peroxisome proliferators. In addition, the peroxisome proliferators PFDA, PFOA, and ciprofibrate induced hepatic ACBP following in vivo administration to rats indicating that this phenomena is not exclusive to in vitro systems. Therefore, ACBP appears to be a member of the peroxisome proliferator loci, a group of lipid metabolizing proteins, including FABP, which are regulated by peroxisome proliferators such as fibric acids and perfluorinated fatty acids.
Test substance : PFOA
06.12.2005 (615)

Endpoint : other: Uncoupling oxidative phosphorylation in rat liver mitochondria
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1967
GLP : no data
Test substance : other TS

Method : The ability was determined of PFOA to uncouple oxidative phosphorylation in rat liver mitochondria oxidizing succinate.
Result : PFOA is capable of uncoupling oxidative phosphorylation in rat liver mitochondria oxidizing succinate. PFOA was more potent in this regard than was octanoic acid [60% inhibition versus 45% for octanoic acid; both acids were tested at 10 x 10-4 M.
Test substance : PFOA
04.11.2005 (625)

Endpoint : other: Apoptosis
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2001
GLP : no data
Test substance : other TS

Method : It has been shown that one of the most potent rodent hepatocarcinogens, PFOA, induces apoptosis in human HepG2 cells in a dose- and time-dependent manner. This study investigated the involvement of reactive oxygen species (ROS), mitochondria, and caspase-9 in PFOA-induced apoptosis.

Result : Treatment with 200 and 400 microM PFOA was found to cause an increase in the cellular content of superoxide anions and hydrogen peroxide after 3 h. Measurement of the mitochondrial transmembrane potential (Delta Psi(m)) after PFOA treatment showed a dissipation of Delta Psi(m) at 3 hours. Caspase-9 activation was seen at 5 h after treatment with 200 microM PFOA. In order to evaluate the importance of these events in PFOA-induced apoptosis, cells were co-treated with PFOA and N-acetylcysteine (NAC), a precursor of glutathione, or Cyclosporin A (CsA), an inhibitor of mitochondrial permeability transition pore (MPT pore). NAC reduced Delta Psi(m) dissipation, caspase 9 activation, and apoptosis, indicating a role for PFOA-induced ROS. In addition, CsA also reduced Delta Psi(m) dissipation, Caspase-9 activation, and apoptosis, indicating a role for PFOA-induced opening of the MPT pore. In summary, a ROS and mitochondria-mediated pathway for induction of apoptosis by PFOA was demonstrated.

Test substance : PFOA

07.12.2005 (490)

Endpoint : other: Apoptosis in human hepatoblastoma cells
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1999
GLP : no data
Test substance : other TS

Method : Treatment of human hepatoblastoma HepG2 cells with PFOA induces apoptosis, as well as perturbing the cell cycle. This apoptosis was characterized by electron microscopy, which revealed typical nucleosomal fragmentation (also observed as a 'DNA ladder' upon electrophoresis on agarose) and was quantitated using propidium iodide staining of cellular DNA and the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay.

Result : This process was dose- and time-dependent: apoptosis became manifest with 200 microM and maximal (45% of the cells) upon exposure to 450 microM PFOA for 24 h. Electrophoresis of the DNA from HepG2 cells

exposed to 500 microM PFOA for 24 h or to 400 microM PFOA for 48 h revealed a smear typical of non-specific degradation. These findings indicate that in the presence of high concentrations of PFOA for long times, HepG2 cells undergo primary and secondary necrosis. Quantitation of trypan blue exclusion supported this conclusion. Flow cytometric analysis revealed that the cell cycle of HepG2 cells was perturbed by exposure to 50-150 microM PFOA. A 50 microM concentration resulted in a significant increase in the proportion of G(2)/M cells and, simultaneously, a decrease in the number of cells in the S phase, whereas treatment with 100 or 150 microM PFOA increased the proportion of cells in the G(0)/G(1) phase and decreased the number of cells in the G(2)/M and S phases. Simultaneous flow cytometric analysis of apoptosis-associated DNA strand breaks using the TUNEL procedure and of propidium iodide staining of cellular DNA revealed DNA breaks in HepG2 cells exposed to 150 microM PFOA, prior to nuclear fragmentation.

Test substance : PFOA

07.12.2005 (548)

Endpoint : other: Depletion of free coenzyme A
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : The purpose of this study was to determine if, as structural fatty acid analogues, perfluorosulfonic acid and perfluorinated carboxylic acids deplete free coenzyme A. Freshly homogenized rat liver was incubated in the presence of the test compound at 37°C for 40 minutes. Caprylic acid was included as a positive control and the concentration of free coenzyme A determined by reversed-phase HPLC. The concentration of free CoA detected in the control incubations was 92.4 +/- 13.6 nmol/g liver.

Result : Incubation with caprylic acid caused a 5% decrease in free CoA, whereas there was a 15%-40% depletion of CoA when liver tissue was incubated with one or another of the perfluorinated acids. We conclude that PFOS and the perfluorinated carboxylic acids, including PFOA, deplete free mitochondrial coenzyme A, and that this may contribute to the mechanism by which these compounds interfere with fatty acid metabolism in vivo.

Test substance : PFOA

07.12.2005 (459)

Endpoint : other: Cell communication
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1987
GLP : no data
Test substance : other TS

Method : The effects of PFOA and PFDA on cell communication between freshly isolated rat hepatocytes and an established rat liver cell line were investigated.
Result : Results indicate that PFDA treatment inhibits cell communication while treatment with PFOA has no effect.
Test substance : PFOA
07.12.2005 (528) (529)

Endpoint : other: Down-regulation of cytochrome P450 2C family members and positive acute-phase response gene expression by peroxisome proliferator chemicals.
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1998
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : In this study, it is shown that peroxisome proliferator chemical (PPC) exposure leads to alterations in the expression of genes in rat liver regulated by the sex-specific growth hormone secretory pattern and induced during inflammation.
Result : Expression of the male-specific cytochrome P450 (P450) 2C11 and alpha2 urinary globulin (alpha2u) genes and the female-specific P450 2C12 gene was down-regulated by some PPC, including PFOA. Expression of P450 2C13, also under control by the sex-specific growth hormone secretory pattern, was not altered by PPC treatment, indicating that regulation of CYP2C family members does not involve perturbation of the growth hormone secretory pattern. In contrast to the increases in expression observed when inflammation was induced in male rats, two positive acute-phase response genes, alpha1-acid glycoprotein and beta-fibrinogen, were decreased by PPC exposure. The down-regulation of the P450 2C11 by WY-14,643 could be reproduced in cultured rat hepatocytes, indicating the down-regulation is a direct effect. Experiments in wild-type mice and mice that lacked a functional peroxisome proliferator-activated receptor-alpha gene showed that down-regulation by WY of alpha1-acid glycoprotein, beta-fibrinogen, and a mouse homologue of alpha2u was dependent on peroxisome proliferator-activated receptor-alpha expression. Our results demonstrate that PPC exposure leads to down-regulation of diverse liver-specific genes, including CYP2C family members important in hormonal homeostasis and acute-phase response genes important in inflammatory responses.
07.12.2005 (139)

Endpoint : other: Down-regulation of gap junctional communication.
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1996
GLP : no data

Test substance : other TS

Method : The down-regulation of gap junction intercellular communication (GJIC) by several oncogenes and non-genotoxic chemicals has been implicated in tumor promotion, teratogenesis, and peripheral neuropathies. The use of biological assays that monitor GJIC can give valuable toxicological information of chemicals and can be used in predictive risk assessment of exposures to toxicants. The scrape loading/dye transfer technique was used to measure GJIC in WB-F344 rat liver epithelial cells.

Result : The jet fuels JP-8 and JP-4 inhibited GJIC at a dose of 10 uL/mL medium. PFDA and PFOA inhibited GJIC at concentrations of 100 and 250 uM, respectively. Inhibition was dose-dependent, reversible, and occurred at non-cytotoxic levels. Quadricyclane was found to be highly cytotoxic and, did not inhibit GJIC. The incubation time required for inhibition of GJIC by the jet fuels was 20 minutes, and 5 minutes for PFDA and PFOA. The short incubation time required for the inhibition of GJIC by perfluoro-fatty acids suggested a membrane-fluidity perturbation mechanism similar to linoleic acid. The perfluoro-fatty acids also inhibited GJIC in a human kidney epithelial cell line, but the jet fuels did not inhibit GJIC in this cell line. This differential effect of jet fuels is a good example of how toxicants, including carcinogens, can be issue and/or species specific.

Test substance : PFOA

07.12.2005 (151)

Endpoint : other: Effects of halogenated fatty acids on recombinant GABA receptors expressed in Xenopis oocytes.

Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1996
GLP : no data
Test substance : other TS

Method : GABA-activated Cl- current was expressed in Xenopus oocytes after injecting cRNA that had been transcribed in vitro from complementary DNA (cDNA) coding for a single GABA rho i-subunit cloned from human retina.

Result : The expressed current was insensitive to 100 microM bicuculline, but was activated by the GABA analogue trans-4-aminocrontonic acid (TACA). Anion-selective permeability of the expressed rho 1-subunit was determined by isotonically replacing the extracellular Cl- with different anions. The anion permeability was very similar to the native GABAA receptor/channel following a sequence of SCN- > I- > NO3- > Br- > or = Cl- . Halogenated fatty acids, such as chlorotrifluoroethylene (CTFE) and perfluorinated oligomer acids inhibited the GABA-induced current in oocytes expressing the human retinal GABA rho 1-subunit or rat brain GABAA receptor alpha 1,beta 2,gamma 2 subunits. The inhibitory effect of halogenated fatty acids demonstrated a carbon chain length-dependent manner of: C10 > C8 > C6 > C4. PFOA was less effective at blocking this channel than the C8-CTFE oligomer acid. Radiolabeled GABA binding assay indicated that CTFE oligomer acids do not interfere at the GABA binding site of the receptor. Furthermore, the C8-CTFE oligomer fatty acid did not compete with picrotoxin for binding sites within the pore of the channel. These studies demonstrated that the heterologous expression system is useful for studying the molecular interaction between potential neurotoxic agents and neuroreceptors. These results provide detailed information that should contribute to our understanding of the structure and

function of retinal GABA receptors.

Test substance : PFOA

07.12.2005 (150)

Endpoint : other: Medical uses
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2004
GLP : no data
Test substance : other TS

Method : PFOA or a salt or an ester thereof, perfluorosuberic acid, perfluoroheptanoic acid, perfluorohexanoic acid, perfluoropentanoic acid, perfluorobutanoic acid, or perfluoropropionic acid or a salt or an ester thereof or perfluorooctane are useful in treating diabetes, obesity, hypercholesterolemia, hyperlipidemia, cancer, inflammation or other conditions in which modulation of lipid or eicosanoid status or function may be desirable. These compounds may be PPAR (particularly PPAR alpha or gamma) modulators or agonists. Particular compounds exemplified are APFO, PFOA, methyl perfluorooctanoate, perfluorooctane, perfluoroheptanoic acid, perfluoropentanoic acid, and perfluoropropionic acid.

Test substance : PFOA or salt or ester thereof

07.12.2005 (245) (634)

Endpoint : other: Medical Uses
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1986
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The fluorine containing acid that can be administered to the body for alleviating symptoms of neoplastic conditions without treating the disease itself include perfluorobutyric acid, perfluoroglutamic acid, PFOA, perfluoropropionic acid, perfluorosuccinic acid, hexafluorophosphoric acid, fluoroacetic acid, fluorobenzoic acid, fluoromethylbenzoic acid, and fluorosulfuric acid. The above fluoroacids are given as representative and the invention does not exclude the use of other fluorine containing acids. The non-toxic salts of esters of the fluorine containing acids can also be employed. The ammonia (NH3) salts are at present preferred. The organic fluorine containing acid can contain various amounts of fluorine atoms, however, a significant decrease in activity appears to result when these acids contain 20 or more fluorine atoms. It is thus advantageous to employ fluorine containing organic acids having less fluorine atoms. Best results to date are obtained with PFOA and hexafluorophosphoric acid, particularly their ammonium salts. The fluorine containing acids can also be used in admixtures with each other.

07.12.2005 (514)

Endpoint : other: Glove permeation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Five types of gloves (neoprene; neo-synthetic latex rubber, floc lined; latex; natural latex; neoprene rubber) were evaluated for their permeation resistance to a 30% aqueous solution or dry powder of APFO. Samples of the gloves were tested in duplicate in 10 mL glass permeation cells with water used as a collection medium on the inside surface of the gloves. A 10 mL aliquot of the collecting medium was analyzed for APFO by spectrophotometry after an 8-hour exposure. Breakthrough was determined when a detectable amount of APFO was found in the collection medium. The minimum detection limit for APFO was 1 ug/mL in the collection medium.

Result : Permeation of five types of gloves by APFO was evaluated. Three of the gloves (Neoprene, neosynthetic latex and natural latex) had a measurable breakthrough time and permeation rate after 8 hours of continuous exposure to a 30% APFO solution.

Results of the tests performed with APFO powder show that in four of the glove samples, no breakthrough was observed after 8 hours of continuous exposure and only a very small amount permeated in the yellow latex sample from Best Manufacturing Company.

07.12.2005 (181)

Endpoint : other: Airborne size distribution of APFO dust atmosphere
Study descr. in chapter : 5.4 Repeated Dose Toxicity
Reference : DuPont Co. (1981) Unpublished Data, Report No. 205-81, Subacute inhalation toxicity of pentadecafluorooctanoic acid, ammonium salt.
Type : other: Airborne size distribution of APFO dust atmosphere
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The 2-week inhalation toxicology study with APFO in rats demonstrated biological correlations between the airborne concentration of APFO and toxicological responses in exposed rats. This study was conducted at 3 exposure concentrations (1, 8, and 80 mg/m3 APFO). However, air sampling techniques employed at that time did not clearly identify the size distribution of the APFO particles in the atmosphere. The following experiment was conducted to determine the airborne size distribution of APFO, using as best as possible, the generating conditions used in the 1980 experiment.

Atmospheres were generated by suspension of APFO in air with a Model 00 Jet-O-Mizer jetmill. APFO was metered into the jetmill with a twin-screw volumetric feeder where it was carried with high-pressure air through a glass cyclone elutriator and an exposure chamber.

The atmospheric concentration of APFO was determined by gravimetric analysis where a measured volume of chamber atmosphere was drawn from the chamber sample port, through a 25 mm filter cassette containing a pre-weighed Gelman glass fiber filter (Type A/E). Filters were weighed on a Cahn Microbalance.

Particle size distribution was determined with a Sierra® Series 210 Cyclone Preseparator/Cascade Impactor and Sierra® Series 110 Constant Flow Air Sampling pump.

Result : Air Sampling Results

Chamber Concentration: 397.7 ± 20.8 mg/m3 APFO (mean ± SD)
Particle Size: 2.6 µm ± 2.17 (MMAD ± GSD)

Conclusion

The geometric standard deviation (GSD) of 2.17 indicates a size distribution that is typical of these types of atmosphere generating systems and suggests a reasonably homogenous atmosphere. Unlike the 1980 study, the current experiment utilized a direct gravimetric method for the particle size distribution determination. The APFO concentration observed in the current study is higher than those used in the 1980 study because of the large amount of set-up time currently required to achieve stable, low level atmospheres. However, the GSD would not be expected to change significantly at lower concentrations.

07.12.2005 (214)

Endpoint : other: Respirator evaluation
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The purpose was to evaluate M.S.A. Combination Type GMA-H respirator cartridges against APFO dust for breakthrough. The cartridge pairs were tested against an average concentration of 0.56 mg/m3 APFO generated in a dust generator, and introduced into an air blow of 60 L/min maintained at 50% relative humidity and ambient room temperature. Both upstream and downstream airborne concentrations were monitored for APFO dust by filter paper cassettes backed up with an impinger sampling train to absorb possible APFO vapors. Aliquots of the aqueous extracts of the filter paper and aliquots of the aqueous impinger samples were analyzed colorimetrically for APFO.

Result : After 40 hours of continuous exposure, no detectable amount of APFO dust or vapor was found downstream on the breathing side of the cartridge pairs tested. The minimum detectable limit was 1.5 ug of APFO. Based on a 420 L air sample, this would calculate to be 0.004 mg/m3. The mean upstream airborne concentrations were 0.67 ± 0.33 and 0.48 ± 0.15 mg/m3 at 40 and 54 hours, respectively. The results demonstrated that the M.S.S.

combination type GMA-H cartridges effectively filter APFO dust and vapor concentrations at the test conditions for a minimum of 40 hours.

07.12.2005 (169)

Endpoint : other: Teflon feeding study
Study descr. in chapter :
Reference :
Type :
Species : rat
Sex :
Strain :
Route of admin. : Oral feeding study
No. of animals :
Vehicle :
Exposure period : 14 day(s)
Frequency of treatm. : Daily
Doses : 25% Teflon with or without APFO
Control group : yes, concurrent no treatment
Observation period :
Result :
Method : other
Year : 1961
GLP : no data
Test substance : other TS

Method : Groups of 6 young adult ChR-CD rats were administered diets containing various Teflon samples for 3 weeks followed by a 2-week recovery period. A control group was administered the same diet to which 25% powdered cellulose had been added. At the end of the study, the animals were sacrificed and their livers weighed.

Result : In a two-week feeding study, 25% Teflon with APFO dispersing agent was administered in the diet of a group of six rats. After a two-week recovery period the treated animals had slightly heavier livers than the controls or animals receiving Teflon without the APFO.

Test substance : Teflon containing APFO; Controls were fed Teflon without APFO or were untreated.

07.12.2005 (158)

Endpoint : other: Biological detergent properties
Study descr. in chapter :
Reference :
Type :
Species :
Sex :
Strain :
Route of admin. :
No. of animals :
Method : other
Year : 1995
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : APFO was investigated, as representative of fluorinated surfactants, in terms of its suitability as a "biological detergent." It did not interfere with the Markwell modification of the Lowry procedure at detergent concentrations of up to 2% (w/v). Critical micellization concentration (cmc) values (0.013-0.0275 M) for this detergent were determined in a number of buffers of biological interest. It was demonstrated that the detergent can be removed by dialysis, albeit slowly. This slow removal may be particularly useful for reconstitution/crystallization studies.

Result : Detergents are important reagents in membrane biochemistry. Since each membrane system studied places different demands on the detergent in

terms of desirous physicochemical properties, detergents new to biochemistry must continuously be sought. APFO was investigated, as representative of fluorinated surfactants, in terms of its suitability as a 'biological detergent'. It did not interfere with the Markwell modification of the Lowry procedure at detergent concentrations of up to 2%. Critical micellization concentration values (0.013-0.0275 M) for this detergent were determined in a number of buffers of biological interest. It was demonstrated that the detergent can be removed by dialysis, albeit slowly. This slow removal may be particularly useful for reconstitution/-crystallization studies. Solubilization studies on several membrane systems containing the proteins listed (the major protein of the membrane sector of the vacuolar H+-ATPase (16 kDa protein); photosystem II; equine herpes virus envelope proteins) indicate that it is a potent solubilizing agent, likely to enhance the yield in cases where solubilization has already been demonstrated and, in other cases, to solubilize proteins formerly recalcitrant to solubilization. The removal of APFO from solubilized 16-kDa protein by means of Extracti-Gel D resin as a means of exchanging detergents quickly and with a minimum requirement for second detergent was investigated.

07.12.2005 (549)

07.12.2005

07.11.2005

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Epidemiology

Method : In a retrospective cohort mortality study, the relationship between mortality and employment at a PFOA production plant were investigated. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983.

Result : In a retrospective cohort mortality study, the relationship between mortality and employment at a PFOA production plant were investigated. The cohort consisted of 2788 male and 749 female workers employed between 1947 and 1983. The all-causes standardized mortality rate (SMR) was 0.75 for men and 0.77 for women. Among men, the cardiovascular SMR was 0.68 and the all-gastrointestinal diseases SMR was 0.57. There was no significantly increased cause-specific SMR for either men or women. The SMRs for prostate cancer were 2.03 in the Chemical Division group (exposed) and 0.58 in the non-Chemical Division group (not exposed to chemicals). In the Chemical Division group there were 4 observed and 2 expected deaths from prostate cancer (Gilliland and Mandel, 1993; J. Occup. Med., 35(9):950-954)). Among men, 10 years of employment in PFOA production was associated with a significant threefold increase in prostate cancer mortality compared to no employment in production. Given the small number of prostate cancer deaths and the natural history of the disease, the association between production work and prostate cancer must be viewed as hypothesis generating and should not be over interpreted. If the prostate cancer mortality excess is related to PFOA, the results of this epidemiology study and the clinical study described above suggest that PFOA may increase prostate cancer mortality through endocrine alterations (Gilliland, 1993; Diss. Abstr., 53(10):5158).

There was no significant association between any cause of death and latency in either the Chemical Division group (exposed) or the non-Chemical Division group (not exposed). In the Chemical Division group, the

SMR for prostate cancer was 1.61 in the greater than 15-year latency group. For all men employed at this plant, 6 deaths were recorded for prostate cancer versus 6 expected. Further research is needed to evaluate and confirm the association between PFOA and prostate cancer (Gilliland and Mandel, 1993). A more thorough examination of these data show no relationship between PFOA and prostate cancer (Olsen, 1996; Personal Communication to R. G. Perkins).

An update of this study was conducted to include the death experience of employees through 1997 (Alexander, 2001a; Final Report. Division of Environmental and Occupational Health, School of Public Health, University of Minnesota (April 26)). The cohort consisted of 3992 workers. The eligibility requirement was increased to 1 year of employment at the Cottage Grove plant, and the exposure categories were changed to be more specific. Workers were placed into 3 exposure groups based on job history information: definite PFOA exposure (n = 492, jobs where cell generation, drying, shipping and packaging of PFOA occurred throughout the history of the plant); probable PFOA exposure (n = 1685, other chemical division jobs where exposure to PFOA was possible but with lower or transient exposures); and not exposed to fluorochemicals (n = 1815, primarily nonchemical division jobs).

In this new cohort, 607 deaths were identified: 46 of these deaths were in the PFOA exposure group, 267 in the probable exposure group, and 294 in the non-exposed group. When all employees were compared to the state mortality rates, SMRs were less than 1 or only slightly higher for all of the causes of death analyzed. None of the SMRs were statistically significant. The highest SMR reported was for bladder cancer (SMR = 1.31). Five deaths were observed (3.83 expected). A few SMRs were elevated for employees in the definite PFOA exposure group: 2 deaths from cancer of the large intestine (SMR = 1.67), 1 from pancreatic cancer (SMR = 1.34), and 1 from prostate cancer (SMR = 1.30). In addition, employees in the definite PFOA exposure group were 2.5 times more likely to die from cerebro-vascular disease (5 deaths observed, 1.94 expected). In the probable exposure group, 3 SMRs should be noted: cancer of the testis and other male genital organs (SMR = 2.75); pancreatic cancer (SMR = 1.24); and malignant melanoma of the skin (SMR = 1.42). Only 1, 6, and 2 cases were observed, respectively. The SMR for prostate cancer in this group was 0.86 (n = 5). There were no notable excesses in SMRs in the non-exposed group, except for cancer of the bladder and other urinary organs. Four cases were observed and only 1.89 were expected.

It is difficult to interpret the results of the prostate cancer deaths between the first study and the update because the exposure categories were modified in the update. Only 1 death was reported in the definite exposure group and 5 were observed in the probable exposure group. All of these deaths would have been placed in the chemical plant employees exposure group in the first study. The number of years that these employees worked at the plant and/or were exposed to PFOA was not reported. This is important because even 1 prostate cancer death in the definite PFOA exposure group resulted in an elevated SMR for the group. Therefore, if any of the employees' exposures were misclassified, the results of the analysis could be altered significantly.

The excess mortality in cerebrovascular disease noted in employees in the definite exposure group was further analyzed based on number of years of employment at the plant. Three of the 5 deaths occurred in workers who were employed in jobs with definite PFOA exposure for more than 5 years but less than 10 years (SMR = 15.03). The other 2 occurred in employees with less than 1 year of definite exposure. The SMR was 6.9 for employees with greater than 5 years of definite PFOA exposure. In order to confirm that the results regarding cerebrovascular disease were not an artifact of

death certificate coding, regional mortality rates were used for the reference population. The results did not change. When these deaths were further analyzed by cumulative exposure (time-weighted according to exposure category), workers with 27 years of exposure in probable PFOA exposed jobs or those with 9 years of definite PFOA exposure were 3.3 times more likely to die of cerebrovascular disease than the general population. A dose-response relationship was not observed with years of exposure.

The slight excess in bladder cancer in the cohort as a whole should be noted given the bladder cancer mortality experience at 3M's Decatur plant, which produces mostly PFOS. Bladder cancer mortality was 4 times higher in workers with high PFOS exposure jobs at 3M's Decatur, AL plant than the general population [SMR = 4.81] (Alexander, 2001b; Final Report. Division of Environmental and Occupational Health, School of Public Health, University of Minnesota (April 26)). Three deaths were reported, and all of them occurred in the high exposure group. Serum PFOA levels in workers are lower at the Decatur plant, where PFOA is used as an elastomer in fluoropolymer production or is produced as a by-product, than at Cottage Grove; however, the manufacture of PFOA began at Decatur in 1999. Therefore, PFOA exposures may increase at this plant. It is not clear whether PFOA, PFOS or some other chemical may be responsible for the bladder cancer deaths observed at these plants; however, follow up should continue in an effort to shed some light on this observation.

It is difficult to compare the results of the first and second mortality studies at the Cottage Grove plant since the exposure categories were modified. Although the authors claim that the newer exposure categories are more accurate, it is still likely that exposure misclassification occurred. Without measured exposures (serum PFOA levels), it is difficult to judge the reliability of the exposure categories that were defined. In the second study, the chemical plant employees were subdivided into PFOA-exposed groups, and the film plant employees essentially remained in the "non-exposed" group. This was an effort to more accurately classify exposures; however, these new categories do not take into account duration of exposure or length of employment. Another limitation to this study is that 17 death certificates were not located for deceased employees and therefore were not included in the study. The inclusion or exclusion of these deaths could greatly change the analyses for the causes of death that had a small number of cases. Follow up of worker mortality at Cottage Grove (and Decatur) needs to continue. Although there were more than 200 additional deaths included in this analysis, it is a small number and the cohort is still relatively young.

Given the results of studies on fluorochemicals in both animals and humans, further analysis is warranted.

07.12.2005 (70) (71) (281) (282) (467)

Type of experience : Human - Epidemiology

Method : A retrospective cohort mortality study was made of employees at a 3M plant where APFO, along with other fluoro compounds, including PFOS, are manufactured. Records on 4218 employees were reviewed. Only those who worked for six months or more (3688 workers) were included in the mortality follow-up.

Result : Records on 4218 employees were reviewed. Only those who worked for six months or more (3688 workers) were included in the mortality follow-up. Of the 180 known deaths, 177 death certificates were obtained. Overall the number of deaths was significantly less than expected. The observed-to-expected ratio for cancer deaths was 1.0.

07.12.2005 (4) (603)

Type of experience : Human - Epidemiology

Method : The mortality experience of a cohort of employees of a perfluorooctanesulfonyl fluoride (POSF) based fluorochemical production facility was evaluated. A retrospective cohort mortality study followed all workers with at least one year of cumulative employment at the facility. The jobs held by cohort members were assigned to one of three exposure subgroups; high-exposed, low-exposed, and non-exposed, based on biological monitoring data for perfluorooctane sulfonate (PFOS). Although POSF-based chemicals are the primary fluorochemicals produced at this plant, exposure to other fluorochemicals including PFOA is likely.

Result : A total of 145 deaths were identified in the 2083 cohort members. Sixty five deaths occurred among workers ever employed in high-exposed jobs. The overall mortality rates for the cohort and the exposure subcohorts were lower than expected in the general population. Two deaths from liver cancer were observed in the workers with at least one year of high- or low-exposure (standardized mortality ratio (SMR) 3.08. The risk of death from bladder cancer was increased for the entire cohort (three observed, SMR 4.81. All three bladder cancers occurred among workers who held a high-exposure job (SMR 12.77). The bladder cancer cases primarily worked in non-production jobs, including maintenance and incinerator and wastewater treatment plant operations. Workers employed in high-exposure jobs had an increased number of deaths from bladder cancer; however it is not clear whether these three cases can be attributed to fluorochemical exposure, an unknown bladder carcinogen encountered during the course of maintenance work, and/or non-occupational exposures. With only three observed cases the possibility of a chance finding cannot be ruled out.

Test substance : PFOA

07.12.2005 (72)

Type of experience : Human - Epidemiology

Result : At a community meeting in Vincent, Ohio, Edward A. Emmett, MD, Professor of Occupational & Environmental Medicine at the University of Pennsylvania School of Medicine, presented the health-related results of an independent, epidemiological study led by him to investigate PFOA levels in the blood of residents of southeastern Ohio. Specifically, Emmett and his colleagues reported no relationship between elevated PFOA levels and blood-test results that would indicate liver damage or a history of liver disease (including cirrhosis, hepatitis, and any other liver condition), or thyroid damage or a history of thyroid disease. The researchers found the highest levels of PFOA were in the most vulnerable populations - namely, children under 6 years of age and seniors over 60 - a situation, said Emmett, that is "the exact opposite of what we would want to see from a public-health perspective." The scientists also reported that PFOA levels in the blood were much lower in those who used bottled or spring water as their primary drinking source; and, for people using private well water, there was a direct correlation between PFOA levels in the water they drank and PFOA levels in their blood (in that higher levels of PFOA in water yielded correspondingly higher levels of PFOA in the blood). The researchers detected no relationship between high PFOA levels in blood serum and alcohol consumption, cigarette smoking, eating fish caught locally, and eating meat or game harvested locally. They did detect a link, however, between the consumption of large quantities of homegrown fruits and vegetables and higher levels of PFOA in the blood. "The nature of this association will require further study," notes Emmett, "since it is not clear if this was due to PFOA in the fruits and vegetables themselves, in the water used for cooking, cleaning, and canning the foods, or if the people eating more homegrown fruits and vegetables had a different diet and/or drinking habits than those who consumed smaller quantities of homegrown fruits and vegetables."

The study - the nation's first government-sponsored epidemiological study of PFOA levels in the blood of 326 volunteer subjects residing in four communities in southeastern Ohio - previously found PFOA levels that were more than 60 to 80 times higher than those typically found in the general population. They further concluded that water was the major source of contamination. Those earlier findings were released July 27, 2005.

All blood samples were run through a battery of carefully-chosen diagnostic tests designed to detect abnormalities in liver, kidney, and thyroid function, as well as cholesterol status. Based on those results, the researchers found no association between elevated PFOA levels and changes in those tests. "We did, however, find the highest elevations of PFOA in the blood serum of young children and older adults, which is of concern since previous studies in animals have shown a possible link between high PFOA levels and developmental and maturation deficiencies," said Emmett. "As a physician and public-health specialist, I urge parents within the study area to consider taking appropriate measures to reduce PFOA levels in their children's blood-serum by using an alternative drinking-water source - such as bottled water -- if their primary residential water-source contains high levels of PFOA. I also advise consideration of the same precaution for pregnant women and women of child-bearing age who may wish to become pregnant."

Although exposure to high concentrations of PFOA over long durations has been shown to cause liver, pancreatic, testicular, and other cancerous tumors in rats, it is not certain that PFOA would cause the same effects in humans. Indeed, an EPA Advisory Panel is currently debating whether PFOA should be considered a likely carcinogen for regulatory purposes.

"Our study did not address the cancer-risk factor," explains Emmett. "However, it should be noted that we found no toxic effects in the livers of residents studied - and that information may be somewhat comforting because there is always substantial liver toxicity in rats whenever PFOA has caused liver tumors in rats." Emmett also pointed out that current cancer statistics show no elevated cancer-risk in Washington County, Ohio - where the Penn study participants reside - and the rest of Ohio.

The researchers recommended the continuation on ongoing efforts to remove PFOA from the area water as expeditiously as possible. They further recommended that residents consider an alternative drinking source if their primary residential water source contains high levels of PFOA. "Alternative water sources -- such as bottled or spring water - should be considered whenever water may be ingested orally - such as when drinking water, making tea or coffee, cooking, making infant formula, or brushing teeth," said Emmett. "Prior research has shown that PFOA does not readily cross human skin, so it's unlikely that a risk is posed by simply showering, bathing, and washing in water containing PFOA," he added.

07.12.2005 (310)

Type of experience : Human - Epidemiology

Method : An investigation into the occurrence of leukemia at the Washington Works site in Parkersburg, WV was begun after employees expressed concern over recent diagnoses of this condition among their coworkers.

Routine surveillance by the Epidemiology Division had not revealed any statistically significant excess incidence of leukemia among Washington Works active employees from 1956 to 1983. There was also no statistically significant excess mortality from the group of lymphatic and hematopoietic tissue malignancies which includes leukemia, among active employees and

pensioners from 1957 to 1984.

Analysis of cases or deaths occurring after 1983 or 1984, respectively, had not yet been accomplished at the time employee concern was raised. This study estimates the number of cases of leukemia expected at the site through 1988 and compares this to the actual number diagnosed. In addition, morbidity was updated through 1989.

Remark : In April 1989, an additional case of acute myelogenous leukemia was diagnosed in a 51-year old male salary employee at Washington Works. We can assume that the expected number of leukemia cases did not increase measurably in this short time period (January 1989 through April 1989).

Observed and estimated expected numbers of leukemia cases with standardized incidence ratios for 1956 through April 1989 are as follows:

Wage: 6 observed, 2.7 expected, ratio 2.2
Salary: 3 observed, 1.5 expected, ratio 2.0
Total: 9 observed, 4.2 expected, ratio 2.1*

* The standardized incidence ratio of 2.1 for the total group is statistically significant at the 10% level (two-tailed test).

With the diagnosis of this additional case, a case control study is being initiated. Although the stastical power of this study will be limited, due to the small number of leukemia cases, a more thorough investigation into possible associations with work area and chemical exposures is warranted.

See DuPont Co. (1991), Unpublished Data, Karns ME and Fayerweather WE, Epidemiology Section, Report S-88, A case-control study of leukemia at the Washington Works site (December 31) for the details of this follow-up study.

Result : Eight cases of leukemia occurred among male Washington Works employees from 1956 to 1988, compared with an estimated 4.2 cases expected. This is not a statistically significant excess. However, 4 cases were diagnosed since the last surveillance period (i.e. during 1984 through 1988) which represents an unusually high incidence. Two of the 4 cases were of acute non-lymphocytic leukemia, 1 of chronic myelogenous leukemia, and 1 of acute, unspecified, leukemia.

Seven of the 8 leukemia cases were deceased by 1988; no additional cases due to this cause were identified through the Epidemiology Section's Mortality Registry. The number of deaths due to the group of lymphatic and hematopoietic cancers was not remarkably different from expected.

Preliminary review of the work histories did not reveal any commonality of exposure. It was recommended that a thorough review of the work areas and potential chemical exposures particularly to benzene and hydrocarbons, be initiated, and that the site be monitored closely for the occurrence of additional cases.

07.12.2005 (196)

Type of experience : Human - Epidemiology

Method : Following a report of a possible excess incidence of leukemia at the Washington Works plant in Parkersburg, WV, reported by Walrath and Cherry (1989), a case-control study was initiated to determine whether the risk of developing leukemia is related to workplace exposures at this plant.

Result : The study found no association between employment at Washington Works in any particular job or area grouping and the risk of developing leukemia. A statistically significant excess of leukemia was observed in

those who worked as custodians or chemists prior to working at Washington Works. These findings are based on few cases so that considerable variability was observed in the estimated odds ratios.

07.12.2005 (197)

Type of experience : Human - Epidemiology

Method : Cancer incidence are reported for active employees at DuPont's Washington Works plant for the 1959-2001 time period and mortality data were reported for active and retired employees for 1957 through 2000.

Result : Cancer cases were identified through a combination of DuPont Company health and insurance claims and the company cancer and mortality registries. Standardized incidence ratios (SIRs) were only calculated for those cancers for which 5 or more cases were observed, which included 14 types of cancers. These types of cancer were colorectal (32 cases), pancreas (9 cases), larynx (6 cases), lung (61 cases in males), malignant melanoma (14 cases in males), female breast (8 cases), prostate (19 cases), kidney (18 cases), bladder (18 cases), brain (8 cases), lymphoid and histiocytic tissue (9 cases), multiple myeloma (7 cases in males), myeloid leukemia (8 cases), and unspecified sites (14 cases in males).

Two of those cancer types were elevated and statistically significant: bladder [SIR = 1.9] and kidney and urinary organs [SIR = 2.3]. All of the reported cases were male. Other cancer types with elevated SIRs but which were not statistically significant included myeloid leukemia [SIR = 2.02], cancer of the larynx [SIR = 1.77], multiple myeloma and immunoproliferative [SIR = 1.72], malignant melanoma of the skin [SIR = 1.3], testicular cancer [SIR = 1.46], and brain cancer [SIR = 1.2]. West Virginia men tend to have higher rates of both kidney and bladder caner. West Virginia women tend to have higher rates of bladder, but not kidney cancer.

In the mortality report, when all the causes of death were reported, standardized mortality ratios [SMRs], adjusted for age and gender, were statistically significant for rheumatic heart disease [SMR = 3.55] and atherosclerosis and aneurysm [SMR = 1.98].

07.12.2005 (218)

Type of experience : Human - Epidemiology

Method : Cancer distribution and cancer prevalence rates were compared in a PFOA-exposed population (residents) to that of the industry cancer registry data from an occupational exposed population and finally to the general population (SEER). A questionnaire was made on 599 residents living near a PFOA using manufacturing plant operated by DuPont. Cancer registry data from the PFOA DuPont workers was made available through discovery in pending litigation against DuPont and was not previously made available to the scientific community for review. The SEER data was used for comparison to the general population.

Result : PFOA is a man-made perfluorooctane chemical, which is also referred to as C8. PFOA is a key ingredient agent in the production of Teflon and other fluorochemical products and is biopersistent. There has been documented chronic exposure to PFOA of the residents near a plant using PFOA and other fluorinated contaminants. This study's aim was to compare cancer distribution and cancer prevalence rates in a PFOA-exposed population (residents) to that of the industry cancer registry data from an occupational exposed population and finally to the general population (SEER). A questionnaire on 599 residents living near a PFOA using manufacturing plant operated by DuPont was used. Cancer registry data from the PFOA DuPont workers was made available through discovery in pending litigation against DuPont and was not previously made available to the scientific community for review. The SEER data was

used for comparison to the general population. The overall cancer prevalence rate is higher in the PFOA-exposed population when compared to the general population. These findings indicate that the PFOA exposed residential population and PFOA-exposed workers have elevated cancer prevalence. Prostate cancer in the residents was proportionately elevated among young age males. Cervix and uterine cancer rates in women were also higher in the resident population compared to the U.S. general population. The distribution of cancers in the residents and workers is different than expected. Of note are the findings of elevated prevalence rates of atypical cancers such as Non-Hodgkin's Leukemia, and Multiple Myeloma. This data suggests that exposure to PFOA may alter cancer distribution in exposed populations (worker and residents) and may be an important risk factor for an excess of cancer cases.

07.12.2005 (143)

Type of experience : Health records from industry

Method : A study was conducted among 115 workers occupationally exposed to PFOA. Hepatic enzymes, lipoproteins, and cholesterol were measured.

Result : Although PFOA is the major organo fluorine compound found in humans, little information is available concerning human response to PFOA exposure. Therefore, a study was conducted among 115 workers occupationally exposed to PFOA (total serum fluorine levels varied between 0 and 26 ppm, with a mean of 3.3 ppm). In an examination of the cross-sectional associations between PFOA and hepatic enzymes, lipoproteins, and cholesterol, there was no significant clinical hepatic toxicity at the PFOA levels observed in this study (Gilliland and Mandel, 1996). Serum PFOA was positively associated with estradiol and negatively associated with free testosterone (TF) but was not significantly associated with luteinizing hormone. The negative association between TF and PFOA was stronger in older men. Thyroid stimulating hormone and PFOA were positively associated. PFOA and prolactin were positively associated in moderate drinkers. The effect of adiposity on serum glutamyl oxaloacetic and glutamyl pyruvic transaminase decreased as PFOA increased. The induction of gamma glutamyl transferase by alcohol was decreased as PFOA increased. The effect of alcohol on HDL was reduced as PFOA increased. A positive association between hemoglobin, mean cellular volume, and leukocyte counts with PFOA was observed. These results suggest that PFOA affects male reproductive hormones and that the liver is not a significant site of toxicity in humans at the PFOA levels observed in this study. However, PFOA appears to modify hepatic and immune responses to xenobiotics (Gilliland, 1993).

07.12.2005 (281) (283)

Type of experience : Health records from industry

Method : Medical surveillance data of male workers involved in ammonium perfluorooctanoate production in 1993 (n=111), 1995 (n=80) and 1997 (n=74) was examined. Serum PFOA was measured by high-performance liquid chromatography mass spectrometry methods. Plasma cholecystokinin was measured (only in 1997) by the use of direct radioimmunoassay. Serum biochemical tests included hepatic enzymes, cholesterol and lipoproteins.

Result : APFO is a potent synthetic surfactant used in industrial applications. It rapidly dissociates in biologic media to perfluorooctanoate, which is the anion of PFOA. PFOA is a peroxisome proliferator known to increase the incidence of hepatic, pancreas and Leydig cell adenomas in rats. The pancreas acinar cell adenomas may be the consequence of a mild but sustained increase of cholecystokinin as a result of hepatic cholestasis. Although no significant clinical hepatic toxicity was observed, PFOA was reported to have modulated hepatic responses to obesity and alcohol consumption among production workers. To further assess these

hypotheses, we examined medical surveillance data of male workers involved in APFO production in 1993 (n=111), 1995 (n=80) and 1997 (n=74). Serum PFOA was measured by high-performance liquid chromatography mass spectrometry methods. Plasma cholecystokinin was measured (only in 1997) by the use of direct radioimmunoassay. Serum biochemical tests included hepatic enzymes, cholesterol and lipoproteins.

Serum PFOA levels, by year, were: 1993 (mean 5.0 ppm, SD 12.2, median 1.1 ppm, range 0.0-80.0 ppm); 1995 (mean 6.8 ppm, SD 16.0, median 1.2 ppm, range 0.0-114.1 ppm); and 1997 (mean 6.4 ppm, SD 14.3, median 1.3 ppm, range 0.1-81.3 ppm). Cholecystokinin values (mean 28.5 pg/mL, SD 17.1, median 22.7 pg/mL, range 8.8-86.7 pg/mL) approximated the assay's reference range (up to 80 pg/mL) for a 12 hour fast and were negatively, not positively, associated with employees' serum PFOA levels. These findings continue to suggest there is no significant clinical hepatic toxicity associated with PFOA levels as measured in this workforce. Unlike a previously reported observation, PFOA did not appear to modulate hepatic responses to either obesity or alcohol consumption. Limitations of these findings include: 1) the cross-sectional design as only 17 subjects were common for the three surveillance years; 2) the voluntary participation that ranged between 50 and 70 percent; and 3) the few subjects with serum levels 10 ppm or more.

07.12.2005 (471)

Type of experience : Health records from industry

Method : A study of blood chemistry (SGOT, LDH, AP, and bilirubin) was made of Washington Works employees potentially exposed to APFO.

Result : A study was made of Washington Works employees potentially exposed to APFO. Results of blood chemistry testing (SGOT, LDH, AP, and bilirubin) indicated no conclusive evidence of an occupationally-related health problem among workers exposed to APFO.

07.12.2005 (171)

Type of experience : Health records from industry

Method : PFOA was measured in the blood serum of potentially exposed workers.

Result : PFOA was measured in the blood serum of potentially exposed workers. Of the 72 samples taken in 2000, the mean serum PFOA concentration was 1.53 ppm with a range of 0.02 to 9.0 ppm. Five samples taken all from workers in one particular job, tested greater than 5 ppm. Because these workers should have the least exposure potential, the cause of these higher concentrations is being investigated. If these data points are eliminated, the mean concentration is reduced to 1.16 ppm with a maximum concentration of 4.9 ppm.

07.12.2005 (208)

Type of experience : Health records from industry

Method : The purpose of this study was to collect data by randomly sampling employees in the 3M Decatur chemical plant in order to determine the distribution of employee serum fluorochemical levels according to demographics, current and longest held jobs, years worked and building locations. In addition, a random sample of the neighboring 3M Decatur film plant employee population, located at the same site, was tested to determine fluorochemical serum levels in order to characterize the differences between the two plant populations.

In the past, employees at the 3M Decatur chemical plant have voluntarily participated in a fluorochemical medical surveillance program. Analysis of the surveillance data has not shown significant associations between the employees' clinical chemistry and hematology tests and either total serum

organic fluorine or serum PFOS (perfluorooctane sulfonate) levels. However, the voluntary nature of the historical medical surveillance program did not provide for a complete understanding of the distribution of fluorochemical serum levels in the Decatur workforce. Therefore, the purpose of this study was to collect data by randomly sampling employees in the Decatur chemical plant in order to determine the distribution of employee serum fluorochemical levels according to demographics, current and longest held jobs, years worked and building locations. In addition, a random sample of the neighboring 3M Decatur film plant employee population, located at the same site, was tested to determine fluorochemical serum levels in order to characterize the differences between the two plant populations.

A total of 232 employees was randomly selected for serum sampling: 186 (80%) participated in the blood collection which occurred in the Fall, 1998. An additional 77 employees requested blood testing for the determination of fluorochemical levels. Of the random sample of employees who participated, 126 were from the chemical plant and 60 from the film plant. There were 61 volunteers from chemical and 16 volunteers from the film plant; thus, all chemical participants numbered 187 employees and all film participants numbered 76 employees. At the time of blood collection, employees responded to a two-page questionnaire that inquired about their current and longest held jobs, the buildings they had worked in (if chemical employees), and possible routes of oral ingestion of fluorochemicals through cigarette smoking, chewing gum, chewing tobacco and hand washing practices.

Sera samples were extracted using an ion pairing extraction procedure. The extracts were quantitatively analyzed for PFOS, PFHS (perfluorohexane sulfonate), PFOA, PFOSAA (N-ethyl perfluorooctanesulfonamido acetate), PFOSA (perfluorooctane sulfonate amide), M570 (N-methyl perfluorooctanesulfonamido acetate) and M556 (perfluorooctanesulfonamido acetate) using high pressure liquid chromatography/electrospray tandem mass spectrometry and evaluated versus an extracted curve. PFOS, PFHS, PFOA, PFOSAA and PFOSA levels were determined by Northwest Bioanalytical Laboratory. M570 and M556 levels were determined by the 3M Environmental Laboratory.

Result : The overall arithmetic means (and range) and the geometric means and (95% confidence integral) of the random sample of chemical employees (n = 126) for the seven fluorochemicals are presented below (in ppm):

Chemical Plant (Arithmetic Mean (and range) and Geometric Mean (and 95% CI)):

PFOS 1.505(0.091-10.600) and 0.941(0.787-1.126)
PFHS 0.345(0.005-1.880) and 0.180(0.145-0.223)
PFOA 1.536(0.021-6.760) and 0.899(0.722-1.120)
PFOSAA 0.023(0.001-0.269) and 0.008(0.006-0.011)
M570 0.151(0.008-0.992) and 0.081(0.067-0.098)
PFOSA 0.062(0.0005-0.612) and 0.013(0.009-0.018)
M556 0.052(0.001-0.406) and 0.022(0.018-0.029)

The overall arithmetic means (and range) and geometric means (95% confidence interval) of the random sample of film plant employees (n = 60) for the seven fluorochemicals are presented below:

Film Plant (Arithmetic Mean (and range) Geometric Mean (and 95% CI)):

PFOS 0.172 (0.015-0.946) and 0.136(0.114-0.161)
PFHS 0.023 (0.001-0.210) and 0.014 (0.011-0.018)
PFOA 0.071 (0.006-0.298) and 0.049 (0.039-0.062)

PFOSAA 0.004 (0.001-0.038) and 0.003 (0.002-0.003)
M570 0.020 (0.001-0.454) and 0.008 (0.006-0.011)
PFOSA 85% of samples<LLOQ* and 85% of samples<LLOQ*
M556 0.008 (0.0001-0.307) and 0.003 (0.002-0.004)

* LLOQ = lower limit of quantitation for PFOSA ranged from 0.001-0.010 ppm

The above values showed high variability according to the employees' demographics, work history and building locations. Among the random sample (n = 126) of chemical employees, cell operators had the highest serum levels of PFOS (geometric mean 1.970 ppm) and PFHS (geometric mean = 0.697 ppm). However, sera from chemical operators and maintenance workers had the highest levels of other fluorochemical analytes, (PFOSAA, M570, PFOSA and M556) a characteristic likely due to their work in Buildings 3 and 4N with fluorochemical alcohols, amides and acrylates. For example, chemical operators had a geometric mean level of 0.131 ppm for M570 compared to 0.033 ppm for cell operators, 0.042 for mill operators and 0.079 ppm for waste operators. PFOA levels were above the geometric mean of 1.000 ppm for employees with current jobs of cell operators (1.428 ppm), chemical operators (1.887 ppm), maintenance workers (1.095 ppm), mill operators (1.266 ppm) and waste operators (1.542 ppm). Employees with the job categories of engineer/lab and secretary had the lowest serum fluoro-chemical levels. PFHS, and to a lesser extent PFOS, were positively associated with years worked in the chemical plant by job categories. We did not observe an association between hand-to-mouth usage or hand cleanliness (frequency of washing hands) and serum fluorochemical levels.

Like than male counterparts, female chemical operators appeared to have increased PFHS levels with years worked. However, unlike their male counterparts, there was no apparent modest linear association between PFOS and years worked among female chemical operators. Whether this is due to different work practices, exposure patterns or pharmacokinetics once absorbed remains to be determined The sample size itself (n = 10 female chemical operators in random sample), is an important, limiting factor in the interpretation of these data.

The data also indicate significantly lower serum fluorochemical levels among employees who have only worked in the film plant (i.e., defined as those employees in the random sample who have worked only in the film plant with no prior work on the D-1 maker located in the film plant or previous work history in the chemical plant. The D 1 maker uses FX 1801, a methyl FOSE amide). There were significantly lower serum fluorochemical levels among these employees who have only worked in the film plant when compared to those who are current chemical plant employees. Comparing the geometric means for each fluoro-chemical from the random sample of chemical operators and those employees who only have worked in the film plant, we observed the following ratios (in ppm: PFOS (1.481/0.110); PFHS (0.428/0.015); PFOA (1.887/0.052); PFOSAA (0.011/0.002); M570 (0.229/0.022); and M556 (0.044/0.003). Except for PFOSAA, the ratios suggest a 10 fold or greater difference between chemical operators and film plant employees who work several hundred yards away from Building 3. This only film plant employee group had a geometric mean value for PFOS that is approximately 3-4 times higher than the pooled geometric mean (0.029 ppm) from 64 samples obtained from 18 U.S. blood banks. Thus it is suspected that occupational exposure to PFOS does occur within the film plant although at much lower levels than among employees working at the chemical plant. Additionally, employees who worked on the D-1 maker have serum PFOS levels approximately 3 times higher than those employees who have never worked on the D-1 maker or never worked in the chemical plant (i.e., the

only film plant employees).

An association between hand-to-mouth usage or hand cleanliness (frequency of washing hands) and serum fluorochemical levels was not observed. It is possible an association might have been masked because industrial hygiene had instituted an aggressive educational campaign several months prior to collection of blood samples in this study; thus current practices may not be indicative of past practices. Because the half-life of PFOS is estimated to be 1000 days or more, such an association may not be discoverable with this study design. A limitation to this study design which must be considered in the interpretation of the data was the inability to more accurately quantify an employee's work history experience. Decatur work history records provide department numbers and job titles but they do not provide information regarding where someone worked (e.g., what building(s) or with what specific fluorochemicals). Self-reported work history information obtained by questionnaire was highly correlated with Decatur work history record information; nevertheless, the specificity of where someone worked and with what chemicals was not known.

Because many operations are in batch mode, the likelihood of determining specificity of historical workload fluorochemical exposure among chemical operators was not possible.

The present study's sera fluorochemical levels, observed by job categories and building locations, strongly support the recommendations from recently conducted industrial hygiene assessments. These recommendations include specific engineering controls to reduce inhalation exposure, appropriate personal protective equipment to prevent overexposure, and appropriate personal hygiene practices among employees to remove skin contaminations.

Finally, PFOS and PFOA serum levels measured in this study are similar to those that have been previously reported via past biennial medical surveillance activities. Results of previous epidemiologic studies have not associated the serum PFOS or PFOA levels observed in this study population with hepatic, lipid or hormone abnormalities.

07.12.2005 (7) (480)

Type of experience : Health records from industry

Method : The serum half life of several fluorochemicals in humans was determined by obtaining and analyzing multiple serial blood samples from Decatur and Cottage Grove fluorochemical production plant retirees.

Result : This is the second interim report for an ongoing study to determine the serum half life of several fluorochemicals in humans by obtaining and analyzing multiple serial blood samples from Decatur and Cottage Grove fluorochemical production plant retirees. A first interim report, issued in June 2000, suggested the serum half life of PFOS in humans was likely in the range of 139 to 640 days, four fold lower than the previously estimated range of 1000 to 1500 days (data derived from a different population of 3 workers). The serum half life for PFOA in these 27 retirees was 344 days (range 109-1308 days). However, the initial interim report was subsequently discounted in a 3M letter to the U.S. EPA. which noted that the first interim report analyzed the serum after each collection period with only one measurement per time period. In an effort to minimize experimental error, including systematic and random error in the analytical method, a more definitive analytical study on nine of the original 27 subjects was initiated. Serum samples collected from each of the nine subjects over four time points spanning 180 days were measured in triplicate, with all time points from each subject being analyzed in the same analytical run.

The results from this second interim analysis (Burris et al., 2002) suggest that the mean serum half life for PFOS was 8.7 years. The mean serum half life for PFOA was 4.37 years (range 1.5-13.49 years). The 2 females had values of 3.1 and 3.9 years. Half life estimates for both PFOS and PFOA remain higher than those reported in laboratory animals.

This self consistent data set based on triplicate analysis of nine retirees allowed for an estimation of the serum fluorochemical half life for PFOS, PFOA and PFHS with several caveats. Chief among these limitations are the following: no effort was made to determine or control for retiree re exposure to PFOS, PFOA or PFHS during the study time period, although retirees were not present in the production plant. Second, because PFOS is a metabolic product of compounds known to be present in the subject's blood, PFOS is possibly being produced in the body during the course of the study. Both exposure to, and metabolic production of target analyses will lead to artificially long half-life estimations.

Retiree serum samples will be collected from the 27 subjects on an annual basis for the next two years. The samples will be stored frozen (-70°C) and not analyzed until sample collection is completed. At that time, it is planned to analyze all study samples, beginning at T0 during the same analytical run to assure that any experimental biases equally affect every serum sample. No further interim reports will be issued until the sample collection and laboratory analysis are completed.

07.12.2005 (10) (20)

Type of experience : Health records from industry

Method : 3M Antwerp (Belgium) and Decatur (Alabama) fluorochemical manufacturing plant employees' sera were quantitatively analyzed for PFOS, PFOA, PFHS (perfluorohexanesulfonate), PFOSAA (N-ethyl perfluorooctanesulfonamido acetate), M570 (N-methyl perfluorooctanesulfonamido acetate), PFOSA (perfluorooctanesulfonateamide), and M556 (perfluorooctanesulfonamido acetate) using high pressure liquid chromatography/electrospray tandem mass spectrometry and evaluated versus an extracted curve from a human serum matrix. A total organic fluorine index was also determined by calculating the percent of each specific fluorochemical's molecular weight that was attributed to organic fluorine and multiplied by the ppm measured for each fluorochemical and then summed across all seven fluorochemicals.

The 3M fluorochemical medical surveillance program is conducted on a routine periodic basis at the company's Antwerp (Belgium) and Decatur (Alabama) fluorochemical manufacturing plants. In the most recent occurrence in 2000, there were 255 Antwerp employees (206 male and 49 female) and 263 Decatur employees (215 male, 48 female) who participated in the program. This represents approximately 75 percent and 50 percent of the eligible employees at these two locations, respectively. Seventy three percent of the participating Antwerp male employees and 75 percent of the Decatur employees were engaged in production activities. Only 12 percent of the participating Antwerp female employees were engaged in production activities compared to 63 percent of the Decatur female employees.

A standard set of hematological and clinical chemistry tests were analyzed.

Statistical analyses were conducted on the entire surveillance population as well as subgroups by gender, production worker (yes/no) and location. Univariate analyses categorized mean levels by serum PFOS quartile distributions. Multivariable regression was used to analyze the clinical chemistry and thyroid hormones as dependent variables in relation to the

independent effects of PFOS, PFOA or TOF adjusted for several demographic variables (age, body mass index, number of alcoholic drinks per day, cigarettes smoked per day and years worked).

Result : Mean serum PFOS levels for Antwerp production and non production male workers were 1.16 and 0.42 ppm, respectively. Among Decatur production and non-production male workers, their mean serum PFOS levels were 1.63 and 0.73 ppm, respectively. Mean serum PFOA levels for Antwerp male production and non production workers were 1.28 and 0.34 ppm, respectively. Among Decatur male production and non production workers, their mean serum PFOA levels were 2.34 and 0.59 ppm, respectively. The mean PFOS and PFOA levels for the Antwerp female employees (primarily non-production) were 0.13 ppm and 0.07 ppm, respectively. The mean PFOS and PFOA levels for Decatur female production and non-production employees were 0.93 and 1.23 ppm, respectively. Separate reports have been written which analyzed the employees' serum levels in relation to their job and building location work assignments as obtained from a self reported work history questionnaire.

There was a modest positive association between PFOS or PFOA with cholesterol as well as a stronger positive association between PFOA and triglycerides. These associations are inconsistent with the known toxicological evidence that has shown the hypolipidemic (not hyper-lipidemic) effect of PFOS (in rats and primates) and PFOA (in rats but no effect in primates) at dosages that produced serum PFOS or PFOA levels higher than those measured in this population. Therefore, it is unlikely the observed positive associations between PPOS or PFOA and lipids are causal. Because of the potential confounding positive association with serum triglycerides, this variable was added to the hepatic clinical chemistry models as an independent variable. In these models, no significant associations were observed with PFOS, PFOA or TOF in relation to alkaline phosphatase, GOT, AST, ALT or total bilirubin. Although T3 was positively associated with PFOA, no other thyroid hormones were associated with PFOS, PFOA or TOF; thus there is unlikely a causal explanation (e.g., hypothyroidism or hyperthyroidism) for this positive T3 association with PFOA. Hematological and urinalysis results were unremarkable.

In summary, the findings from the 2000 fluorochemical medical surveillance program continue to suggest that Antwerp and Decatur fluorochemical production and non-production employees do not have significant changes in serum cholesterol, lipoproteins or hepatic enzymes that are consistent with toxicological findings in laboratory animals. Limitations of the study include its cross sectional design, the voluntary participation rates, and the lower levels of serum PFOS and PFOA measured among these employees compared with those suspected to cause effects in laboratory animals. A longitudinal analysis is reported separately for the fluorochemical medical surveillance Antwerp and Decatur program data from 1994 to 2000.

07.12.2005 (12)

Type of experience : Health records from industry

Method : The 3M fluorochemical medical surveillance program was conducted in 1994/95, 1997 and 2000 at the company's Antwerp (Belgium) and Decatur (Alabama) manufacturing plants. Serum PFOS and PFOA were assayed in each surveillance program year although the method of analysis (high performance liquid chromatography mass spectrometry) differed slightly between years. A different research laboratory was used to assay PFOS and PFOA in each year. Although cross sectional assessments of the data have been reported, the opportunity to conduct a longitudinal assessment became possible as a result of a large number of employee participants in the 2000 fluorochemical medical surveillance program. A total of 175 male employees voluntarily participated in the 2000 program and at least one of

the two previous program years. A total of 106 (61%) of the 175 employees participated in the 1994/95 program and 110 (63%) of the 175 participated in the 1997 program. Of these 175 employees, a total of 41 (24%) participated in all three years (Antwerp = 21, Decatur = 20), 65 (37%) participated in 1994/95 and 2000 (Antwerp = 45, Decatur = 20) and 69 (39%) participated in 1997 and 9000 (Antwerp = 34, Decatur = 35). There were insufficient number of female employees to conduct any meaningful longitudinal assessment. Only 14 female employees participated in the 2000 fluorochemical medical surveillance program and al least one of the previous program years.

The same hospital laboratory analyzed the clinical chemistries for all three surveillance years. These included: cholesterol, high density lipoproteins (HDL) and triglycerides; alkaline phosphatase, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin. Most reference ranges remained relatively constant over time except for ALT. In each surveillance year, potential confounding factors were also determined. These covariates included age, body mass index, number of alcoholic drinks per day and cigarettes smoked per day.

The continuous outcomes of lipid and hepatic clinical chemistry tests were evaluated as repeated measures incorporating the random subject effect fitted to a mixed model by the MIXED procedure in the SAS statistical package. Restricted maximum likelihood estimates of variance parameters were computed. Adjusted regression models were built by introducing all covariates and testing the covariance structure.

Result : There was a positive association between PFOA and serum cholesterol and triglycerides over time but not with PFOS. This association was limited to the Antwerp employees and, in particular, the 21 Antwerp employees who participated in all three surveillance years. This positive association between PFOA and serum lipids is opposite the inconsistent toxicological evidence that suggested a possible hypolipidemic effect of PFOA in rodents and no effect in primates. Adjusting for potential confounders, there were no temporal changes associated with the fluorochemical tests, PFOS, PFOA and TOF, and the hepatic clinical chemistry tests.

Limitations of this study included the number of employees with three years of surveillance data (only 24% of the 175 subjects), the inability to analyze temporal changes due to small numbers in female employees, the use of different laboratories and the associated systematic (experimental error) with each fluorochemical assay for the three surveillance program years and the lower levels of serum PFOS and PFOA measured in each program year among these employees compared with those that cause effects in laboratory animals.

16.11.2005 (13)

Type of experience : Health records from industry

Result : PFOA has been determined in the serum of several hundred workers employed in industries wherein APFO is used. Serum levels range from less than 0.5 ppb up to 7160 ppb.

08.11.2005 (233) (234) (235) (239)

Type of experience : Health records from industry

Method : This study of 115 occupationally exposed workers examined the cross-sectional associations between PFOA and hepatic enzymes, lipoproteins, and cholesterol.

Result : The findings indicate that there is no significant clinical hepatic toxicity at the PFOA levels observed in this study. PFOA may modulate the previously described hepatic responses to obesity and xenobiotics.

Test substance : PFOA
04.11.2005 (283)

Type of experience : Health records from industry

Method : Mean serum PFOA levels were determined at both the Cottage Grove and Decatur plants since 1993. The latest sample was in 1997 at the Cottage Grove plant. Only 74 employees participated in the 1997 surveillance. The total number of employees working at the plant was not reported. At the Decatur plant, 263 of 500 employees participated in 2000.

Result : Mean serum PFOA levels have increased slightly at both the Cottage Grove and Decatur plants since 1993. Workers at the Cottage Grove plant, where PFOA exposures are highest, have the highest PFOA serum levels. The latest sample was in 1997. The mean serum PFOA level was 6.4 ppm (range = 0.1 - 81.3 ppm). Only 74 employees participated in the 1997 surveillance. The total number of employees working at the plant was not reported. At the Decatur plant, 263 of 500 employees participated in 2000. The mean serum PFOA level was 1.78 ppm. It was higher in males (n = 215) than females (n = 48), 1.90 and 1.23 ppm, respectively. In addition, male production employees had higher mean serum levels (2.34 ppm). Five employees had serum levels greater than 5 ppm, the Biological Limit Value established by the 3M Exposure Guideline Committee. Cell operators had the largest increase in serum PFOA between 1998 and 2000. The highest level was in a chemical operator on the Scotchgard team (12.70 ppm). The mean level for the rest of the members of the team was 5.06 ppm (range 5 - 9 ppm). Other job categories did not exhibit such a large increase. 3M reports that this is due to increased PFOA production at the Decatur plant beginning in 1999. Serum PFOA levels for the Antwerp plant are lower than at Decatur or Cottage Grove, and have decreased slightly since 1995. Participation in medical surveillance at the Antwerp plant was the highest it had ever been in 2000 (258 volunteers out of 340 workers). The mean serum PFOA level was 0.84 ppm, and the highest serum level reported was 7.04 ppm. As in the Decatur plant, males (n = 209) had higher mean serum PFOA levels (1.03 ppm) than females (n = 49, 0.07 ppm). Three employees had levels greater than 5 ppm. 3M's Specialty Materials Manufacturing Division Laboratories, where employees perform fluorochemical research (Building 236), conducted voluntary biomonitoring of 45 employees in 2000. The mean PFOA serum level was 0.106 ppm (range 0.008 - 0.668 ppm). Serum PFOA levels in corporate staff and managers at a 3M plant in St. Paul, MN, where occupational exposure to PFOA should not have occurred, were reported. Four of 31 employees had serum PFOA levels greater than the detection limit of 10 ppb. The mean for these employees was 12.5 ppb. Data on PFOA levels in the general population are very limited. They are very recent so that trends over time cannot be established. The mean serum PFOA levels are lower in the general population than in workers exposed to PFOA.

Test substance : PFOA
08.11.2005 (6) (9) (470) (481) (482) (483)

Type of experience : Health records from industry

Method : In order to gain additional insight into the effects of fluorochemical exposure on workers' health, an "episode of care" analysis was undertaken at 3M's Decatur plant to screen for morbidity outcomes that may be associated with long-term, high exposure to fluorochemicals. An "episode of care" is a series of health care services provided from the start of a particular disease or condition until solution or resolution of that problem. Episodes of care were identified in employees' health claims records using Clinical Care Groups (CCG) software. All inpatient and outpatient visits to health care providers, procedures, ancillary services and prescription drugs used in the diagnosis, treatment, and management of over 400 diseases or conditions were tracked.

Episodes of care were analyzed for 652 chemical employees and 659 film plant employees who worked at the Decatur plant for at least 1 year between January 1, 1993 and December 31, 1998. Based on work history records, employees were placed into different comparison groups: Group A consisted of all film and chemical plant workers; Group B had employees who only worked in either the film or chemical plant; Group C consisted of employees who worked in jobs with high POSF exposures; and Group D had employees who worked in high exposures in the chemical plant for 10 years or more prior to the onset of the study. Film plant employees were considered to have little or no fluorochemical exposure, while chemical plant employees were assumed to have the highest exposures.

Ratios of observed to expected episodes of care were calculated for each plant. Expected numbers were based on 3M's employee population experience using indirect standardization techniques. A ratio of the chemical plant's observed to expected experience divided by the film plant's observed to expected experience was calculated to provide a relative risk ratio for each episode of care (RREpC). 95% confidence intervals were calculated for each RREpC. Episodes of care that were of greatest interest were those which had been reported in animal or epidemiologic literature on PFOS and PFOA: liver and bladder cancer, endocrine disorders involving the thyroid gland and lipid metabolism, disorders of the liver and biliary tract, and reproductive disorders.

Result : The only increased risk of episodes for these conditions of a priori interest were for neoplasms of the male reproductive system and for the overall category of cancers and benign growths (which included cancer of the male reproductive system). There was an increased risk of episodes for the overall cancer category for all 4 comparison groups. The risk ratio was greatest in the group of employees with the highest and longest exposures to fluorochemicals (RREpC = 1.6). Increased risk of episodes in long-time, high-exposure employees also was reported for male reproductive cancers (RREpC = 9.7). It should be noted that the confidence interval is very wide for male reproductive cancers and the sub-category of prostate cancer. Five episodes of care were observed for reproductive cancers in chemical plant employees (1.8 expected), of which 4 were prostate cancers. One episode of prostate cancer was observed in film plant employees (3.4 expected). This finding should be noted because an excess in prostate cancer mortality was observed in the Cottage Grove plant mortality study when there were only 2 exposure categories (chemical plant employees and film plant employees). The update of the study sub-divided the chemical plant employees and did not confirm this finding when exposures were divided into definitely exposed and probably exposed employees.

There was an increased risk of episodes for neoplasms of the gastrointestinal tract in the high exposure group (RREpC = 1.8) and the long-term employment, high exposure group (RREpC = 2.9). Most of the episodes were attributable to benign colonic polyps. Similar numbers of episodes were reported in film and chemical plant employees.

In the entire cohort, only 1 episode of care was reported for liver cancer (0.6 expected) and 1 for bladder cancer (1.5 expected). Both occurred in film plant employees. Only 2 cases of cirrhosis of the liver were observed (0.9 expected), both in the chemical plant. There was a greater risk of lower urinary tract infections in chemical plant employees, but they were mostly due to recurring episodes of care by the same employees. It is difficult to draw any conclusions about these observations, given the small number of episodes reported.

Chemical plant employees in the high exposure, long-term employment group were 2.5 times more likely to seek care for disorders of the biliary tract than their counterparts in the film plant (RREpC = 2.6). Eighteen

episodes of care were observed in chemical plant employees and 14 in film plant workers. The sub-categories that influenced this observation were episodes of cholelithiasis with acute cholecystitis and cholelithiasis with chronic or unspecified cholecystitis. Most of the observed cases occurred in chemical plant employees. Risk ratios of episodes of care for endocrine disorders, which included subcategories of thyroid disease, diabetes, hyperlipidemia, and other endocrine or nutritional disorders, were not elevated in the comparison groups. Conditions which were not identified a priori but which excluded the null hypothesis in the 95% confidence interval for the high exposure, long-term employment group included: disorders of the pancreas, cystitis, and lower urinary tract infections.

The results of this study only should be used for hypothesis generation. Although the episode of care design allowed for a direct comparison of workers with similar demographics but different exposures, there are many limitations to this design. The limitations include: 1) episodes of care are reported, not disease incidence, 2) the data are difficult to interpret because a large RREpC may not necessarily indicate high risk of incidence of disease, 3) many of the risk ratios for episodes of care had very wide confidence intervals, thereby providing unstable results, 4) the analysis was limited to 6 years, 5) the utilization of health care services may reflect local medical practice patterns, 6) individuals may be counted more than once in the database because they can be categorized under larger or smaller disease classifications, 7) episodes of care may include the same individual several times, 8) not all employees were included in the database, such as those on long-term disability, 9) the analysis may be limited by the software used, which may misclassify episodes of care, 10) the software may assign 2 different diagnoses to the same episode, and 11) certain services, such as lab procedures may not have been reported in the database.

Test substance : PFOA
08.11.2005 (468) (469)

Type of experience : Health records from industry

Method : Male and female employees of two perfluorooctanyl-manufacturing locations (Antwerp, Belgium and Decatur, Alabama) participated in a periodic medical surveillance program that included hematology, clinical chemistry, thyroid hormone, and urinalysis testing. Serum concentrations of PFOS and PFOA were measured via mass spectrometry methods.

Result : The mean serum PFOS and PFOA concentrations for 263 Decatur employees were 1.32 ppm and 1.78 ppm, respectively. Mean concentrations were approximately 50% lower among 255 Antwerp workers. Adjusting for potential confounding factors, there were no substantial changes in hematological, lipid, hepatic, thyroid, or urinary parameters consistent with the known toxicological effects of PFOS or PFOA in cross-sectional or longitudinal analyses of the workers' measured serum fluorochemical concentrations.

Test substance : PFOA
07.12.2005 (472)

Type of experience : Health records from industry

Method : Endocrine effects have been associated with PFOA exposure in animals; therefore, 2 cross-sectional studies were conducted on employees of a plant producing PFOA. Medical surveillance, hormone testing and PFOA serum levels were obtained for volunteer workers in 1993 (n = 111) and 1995 (n = 80). Sixty-eight employees were common to both sampling periods.

Eleven hormones were assayed from the serum samples. They were: cortisol, dehydroepiandrosterone sulfate (DHEAS), estradiol, FSH, 17

gamma-hydroxyprogesterone (17-HP), free testosterone, total testosterone, LH, prolactin, thyroid-stimulating hormone (TSH) and sex hormone-binding globulin (SHBG). Employees were placed into 4 exposure categories based on their serum PFOA levels: 0-1 ppm, 1- < 10 ppm, 10- < 30 ppm, and >30 ppm. Statistical methods used to compare PFOA levels and hormone values included: multivariable regression analysis, ANOVA, and Pearson correlation coefficients.

In 1997, voluntary medical surveillance was again offered to employees. In this sampling period, cholecystokinin (CCK) levels were analyzed in 74 employees to determine if they were positively associated with serum PFOA levels. CCK levels were observed because research has suggested that pancreas acinar cell adenomas seen in rats exposed to PFOA may be the result of increased CCK levels. Seventeen of the subjects were common to all three sampling periods (1993, 1995, and 1997). The same statistical methods were used in this study period as used in 1993 and 1995, and the four PFOA exposure categories were also the same.

Result : PFOA was not highly correlated with any of the hormones or with the following covariates: age, alcohol consumption, BMI, or cigarettes. Most of the employees had PFOA serum levels less than 10 ppm. In 1993, only 12 employees had serum levels > 10 ppm, and 15 in 1995. These levels ranged from approximately 10 ppm to over 114 ppm. There were 4 employees in the >30 ppm PFOA group in 1993 and 5 in 1995. Therefore, it is likely that there was not enough power to detect differences in either of the highest categories. The mean age of the employees in the highest exposure category was the lowest in both 1993 and 1995 (33.3 years and 38.2 years, respectively). Although not significantly different from the other categories, BMI was slightly higher in the highest PFOA category. Estradiol was highly correlated with BMI (r = .41 in 1993 and r = .30 in 1995). In 1995, all 5 employees with PFOA levels > 30 ppm had BMIs > 28, although this effect was not observed in 1993. Estradiol levels in the >30 ppm group in both years were 10% higher than the other PFOA groups; however, the difference was not statistically significant. It was postulated that the study may not have been sensitive enough to detect an association between PFOA and estradiol because measured serum PFOA levels were likely below the observable effect levels suggested in animal studies (55 ppm PFOA in the CD rat). Only 3 employees in this study had PFOA serum levels this high. They also suggest that the higher estradiol levels in the highest exposure category could suggest a threshold relationship between PFOA and estradiol.

Note: In 1993, the range of PFOA detection was 0-80 ppm (although 80 ppm was the limit of detection that year, so it could have been higher) and 0-115 ppm in 1995 using thermospray mass spectrophotometry assay.

Free testosterone was highly correlated with age in both 1993 and 1995. A negative association between PFOA serum levels and testosterone was not reported. There were no statistically significant trends noted for PFOA and either bound or free testosterone. However, 17-HP, a precursor of testosterone, was highest in the >30 ppm PFOA group in both 1993 and 1995. In 1995, PFOA was significantly associated with 17-HP in regression models adjusted for possible confounders. However, it is stated that this association was based on the results of one employee (data were not provided in the report). There were no significant associations between PFOA and cortisol, DHEAS, FSH, LH, and SHBG.

There are several design issues that should be noted when evaluating the results of this study. First, although there were 2 study years (1993 and 1995), the populations were not independent. Sixty-eight employees participated in both years. Second, there were 31 fewer employees who participated in the study in 1995, thus reducing the power of the study. There were also very few employees in either year with serum PFOA levels

greater than 10 ppm. Third, the cross-sectional design of the study does not allow for analysis of temporality of an association. Since the half-life of PFOA is at least 1 year, the authors suggest that it is possible that there may be some biological accommodation to the effects of PFOA. Fourth, only one sample was taken for each hormone for each of the study years. In order to get more accurate measurements for some of the hormones, pooled blood taken in a short time period should have been used for each participant. Fifth, some of the associations that were measured in this study were done based on the results of an earlier paper that linked PFOA with increased estradiol and decreased testosterone levels. However, total serum organic fluorine was measured in that study instead of PFOA, making it difficult to compare the results. Finally, there may have been some measurement error of some of the confounding variables.

The mean PFOA serum level in employees participating in the 1997 study period was 6.4 ppm (range 0.1 - 81.3 ppm). The mean CCK value was 28.5 pg/mL (range 8.8 - 86.7 pg/mL). The highest CCK values were reported in the 2 exposure categories less than 10 ppm. The means were 50% higher in these 2 categories than in the categories greater than 10 ppm. When adjusted for potential confounders, multivariable regression models indicated a weak negative association between CCK and PFOA; however, the data were not included in the report. The same methodological issues apply to this portion of the study as well.

Test substance : PFOA
08.12.2005 (470) (476)

Type of experience : Health records from industry

Method : 131 male and 17 female employees participated in the fluorochemical surveillance program. Lipid, hepatic, and thyroid hormone tests were conducted.

Result : Among the men, serum PFOA concentrations were log normally distributed and ranged from 0.007 to 92.03 ppm with a geometric mean of 0.85 ppm. The 17 female employee's serum PFOA concentrations ranged from 0.04 to 4.73 ppm with a geometric mean of 0.42 ppm. There was no statistically significant differences in lipid, hepatic, and thyroid hormone test results among male or female employees. There were no statistically significant differences in the percentage of test results that were above or below the reference ranges of the clinical chemistry and thyroid parameters. Higher serum PFOA concentrations were associated with the specific area where APFO was produced. Employees' serum PFOA concentrations were not correlated with the number of years that they have worked in the Chemical Division at this manufacturing site.

Test substance : PFOA
07.11.2005 (23)

Type of experience : Health records from industry

Method : 54 3M Decatur plant employees voluntarily participated in the fluorochemical medical surveillance program. As part of this program, a blood sample was collected from each participating employee for determination of 5 serum fluorochemicals [PFOS, PFOSAA, M570, PFOA, and PFHS].

Result : The serum PFOS concentrations ranged from 0.082 to 4.2580 ppm with an arithmetic mean of 1.621 ppm and a geometric mean of 1.008 ppm. None of the employees tested had serum concentrations that exceeded the Biologic Limit Value of 5 ppm for PFOA [range 0.025-4.810 ppm; arithmetic mean of 1.497 ppm and a geometric mean of 0.713 ppm]. Comparison of the employees' 2002 serum fluorochemical concentrations with the most recent measurements suggested a decline in concentrations for PFOA, PFHS, PFOSAA, and M570. A decline in serum PFOS concentrations was not observed.

Test substance : PFOA
07.11.2005 (22)

Type of experience : Health records from industry

Method : 38 Cottage Grove employees voluntarily participated in the fluorochemical medical surveillance program. As part of this program, a blood sample was collected from each participating employee for determination of 2 serum fluorochemicals: PFOA and PFOS.

Result : The serum PFOA concentrations ranged from 0.07 to 32.6 ppm with an arithmetic mean of 4.325 ppm and a geometric mean of 1.665 ppm. Eleven participants' serum PFOA concentration exceeded the Biologic Limit Value of 5 ppm for PFOA. Serum PFOS concentrations ranged from 0.050 to 1.170 ppm with an arithmetic mean of 0.334 ppm and a geometric mean of 0.254 ppm. The differences between 2002 PFOA and PFOS serum concentrations and their most recent prior measurements (collected since 2000) resulted in a mean decline of approximately 0.2 ppm for both fluorochemicals.

Test substance : PFOA
07.11.2005 (21)

08.12.2005

Type of experience : Health records from industry

Method : DuPont has been measuring PFOA in workers' blood serum since 1981. Prior to 1981, total blood fluoride levels were reported. All of DuPont's operations in the U.S. that use PFOA with significant exposure potential are concentrated at the Washington Works plant in Washington, WV. PFOA is used as a fluoropolymer reaction aid at this plant. The data presented here reflect serum concentrations of volunteer workers in the plant who had potential PFOA exposure. With the exception of the 2000 sampling period, the same workers were common to all of the other sampling periods, with additional workers participating in 1995.

Result : Year (n = workers); Arithmetic Mean; and Range

2000 (n = 72); 1.53 ppm; and 0.02-9.0 ppm
1995 (n = 80); 1.56 ppm; and 0.12-4.5 ppm
1989-90 (n = 22); 1.96 ppm; and 0.06-11 ppm
1985 (n = 22); 2.34 ppm; and 0.06-18 ppm
1984 (n = 19); 3.21 ppm; and 0.07-24 ppm

08.12.2005 (209)

Type of experience : Human - Medical Data

Method : Health screening examinations, including clinical laboratory tests and blood levels of organic fluorine, were offered to the employees of a 3M plant that produced APFO as well as other fluorochemicals.

Result : Health screening examinations were offered to the employees of a 3M plant that produced APFO as well as other fluorochemicals. No health problems related to exposure to fluorochemicals were encountered among those examined. Additionally, no relationship was observed between deviations from normal between laboratory test results and blood levels of organic fluorine (the liver enzyme SGGT was the most frequently encountered test result exceeding the normal range). APFO exposure levels ranged from 0.03 to 7.6 mg/m3.

08.12.2005 (603)

Type of experience : Human - Medical Data

Method : PFOS and PFHS were analyzed in samples of sera collected from children

between the ages of 6 and 12. Additionally, samples were screened to provide quantitative data on the presence of several other fluorochemicals including PFDS, PFOSA, PFOSAA, M556, M570, PFOA, M463, and M513.

Result : PFOS and PFHS were analyzed in samples of sera collected from children between the ages of 6 and 12. Additionally, samples were screened to provide quantitative data on the presence of several other fluorochemicals including PFDS, PFOSA, PFOSAA, M556, M570, PFOA, M463, and M513. PFOS, PFHS, PFDS, PFOA, AND M463 were detected in each of the samples analyzed. The estimated detection limit is 3 ppb. The average PFOS concentration was 54 ppb, covering a range of 31-115 ppb.

08.12.2005 (8)

Type of experience : Human - Medical Data

Method : In this study, concentrations of PFOS, PFHxS, PFOA, and PFOSA were measured in 473 human blood/serum/plasma samples collected from the United States, Colombia, Brazil, Belgium, Italy, Poland, India, Malaysia, and Korea.

Result : Perfluorooctanesulfonyl fluoride based compounds have been used in a wide variety of consumer products, such as carpets, upholstery, and textiles. These compounds degrade to perfluorooctanesulfonate (PFOS), a persistent metabolite that accumulates in tissues of humans and wildlife. Previous studies have reported the occurrence of PFOS, perfluorohexanesulfonate (PFHxS), PFOA, and perfluorooctanesulfonamide (PFOSA) in human sera collected from the United States. Among the four perfluorochemicals measured, PFOS was the predominant compound found in blood. Concentrations of PFOS were the highest in the samples collected from the United States and Poland (>30 ng/mL); moderate in Korea, Belgium, Malaysia, Brazil, Italy, and Colombia (3 to 29 ng/mL); and lowest in India (<3 ng/mL). PFOA was the next most abundant perfluorochemical in blood samples, although the frequency of occurrence of this compound was relatively low. No age- or gender-related differences in the concentrations of PFOS and PFOA were found in serum samples. The degree of association between the concentrations of four perfluorochemicals varied, depending on the origin of the samples. These results suggested the existence of sources with varying levels and compositions of perfluorochemicals, and differences in exposure patterns to these chemicals, in various countries. In addition to the four target fluorochemicals measured, qualitative analysis of selected blood samples showed the presence of other perfluorochemicals such as perfluorodecanesulfonate (PFDS), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorododecanoic acid (PFDoA), and perfluoroundecanoic acid (PFUnDA) in serum samples, at concentrations approximately 5- to 10-fold lower than the concentration of PFOS. Further studies should focus on identifying sources and pathways of human exposure to perfluorochemicals.

08.12.2005 (349)

Type of experience : Human - Medical Data

Method : The purpose of this investigation was to determine whether there has been a change in the human blood concentration of perfluorooctanesulfonate (PFOS), PFOA, and five other fluorochemicals since 1974.

Blood samples were collected in 1974 (serum) and 1989 (plasma) from volunteer participants of a large community health study. The study included a total of 356 samples (178 from each time period). These samples were analyzed by high-pressure liquid chromatography/tandem mass spectrometry methods.

Result : The median 1974 and 1989 fluorochemical concentrations, respectively, were as follows: PFOS, 29.5 ng/mL vs. 34.7 ng/mL; PFOA, 2.3 ng/mL vs.

5.6 ng/mL; perfluorohexanesulfonate (PFHS), 1.6 ng/mL vs. 2.4 ng/mL; and N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA), less than the lower limit of quantitation (LLOQ; 1.6 ng/mL, vs. 3.4 ng/mL). For N-methyl perfluorooctanesulfonamidoacetate (M570), perfluorooctanesulfonamide, and perfluorooctanesulfonamidoacetate, median serum concentrations in both years were less than the LLOQ values (1.0, 1.0, and 2.5 ng/mL, respectively). Statistical analysis of 58 paired samples indicated that serum concentrations of PFOS, PFOSAA, PFOA, PFHS, and M570 were significantly higher in 1989 than in 1974. The data from 1989 were then compared with geometric mean fluorochemical concentrations of serum samples collected in 2001 from 108 American Red Cross adult blood donors from the same region. Except for M570, there were no statistically significant geometric mean fluorochemical concentration differences between the 1989 and 2001 samples. In conclusion, based on this study population, PFOS and other serum fluorochemical concentrations have increased between 1974 and 1989. Comparison with other regional data collected in 2001 did not suggest a continued increase in concentrations since 1989.

08.12.2005 (479)

Type of experience : Direct observation, other

Method : This study assed the long-term trend of PFOS and PFOA exposures using serum samples collected from late 1970s to 2003 in Japan. Serum samples were collected in Miyagi (Miyagi samples), Akita (Akita samples) and Kyoto (Kyoto samples). In Miyagi, Akita, and Kyoto, samples were collected in 1970s and 2003, in the early 1990s and 2003, and in 2002 and 2003, respectively. 0.5 mL of serum was used for determination of PFOA and PFOS by LC/MS.

Result : The PFOS and PFOA levels in serums (PFOS and PFOA in order ug/L) were; in Miyagi samples in 1970s 1.1 and 0.2 for females (n=40); in 2003 5.7 and 3.3 for males (n=32) and 3.5 and 2.8 for females (n=23). In Akita samples they were; in 1991, 10.2 and 2.2 for males (n=16) and 8.0 and 1.7 for females (n=40) and in 2003 12.9 and 3.4 for males (n=66) and 5.0 and 2.4 for females (n=54). In Kyoto, they were in 2003; 21.8 and 9.4 for males (n=28) and 12.7 and 6.1 for females (n=26). In Miyagi, PFOS and PFOA concentrations have increased 3 times and 14 times, respectively. In Akita, there was no increase between the 1990s and 2003 for PFOS but the level of PFOA was increasing. There are large gender differences in the concentrations of PFOS and PFOA at three locations. Furthermore, there are predominant regional differences for both PFOS and PFOA concentrations.

Test substance : PFOA

08.12.2005 (307)

Type of experience : Direct observation, other

Method : The concentrations of perfluorooctanesulfonylfluoride (POSF), perfluorohexanesulfonate (PFHxS), PFOA, and perfluorooctanesulfonamide (PFOSA) were measured in the blood sera of the general population from the USA, Italy, and India.

Result : PFOS was the most frequently detected compound in the sera. Mean PFOS concentration in US donors was 32.6 ng/mL. PFOS concentrations in Italian and Indian sera were 7.5- and 20 to 30-fold lower, respectively. Levels of PFHxS in the sera of US and Italian donors were 8-10-fold and 2-fold, respectively, less than that of PFOS concentrations. PFOA and PFOSA were found more frequently in the sera of US donors than in the samples of Italy and India.

Test substance : PFOA

08.12.2005 (351)

Type of experience : Direct observation, other

Method : Blood samples from 26 people, 24 Japanese and 2 foreigners from Asian countries, were analyzed.

Result : Levels of PFOS and PFOSA were in the range of 2.0-20.2 and < 1.3-4.8 ng/mL in whole blood, respectively. PFOA concentrations were less than the limit of quantitation (LOQ) of 3.35 ng/mL in whole blood. When the serum concentration was calculated and compared with that of the US sera, the value for the Japanese was about half of the US sera. This shows, on one hand, that the Japanese are less exposed to PFOS compared with Americans, probably because major Japanese producers of perfluorinated surfactants do not use PFOS derivatives as intermediates. On the other hand, it shows that Japanese are exposed to PFOS probably through imported products and/or global scale environmental transport.

Test substance : PFOA

08.12.2005 (434)

Type of experience : Direct observation, other

Method : PFOA concentrations were analyzed in human sera and liver samples. Thirty-one donor samples were obtained from 16 males and 15 females over an 18-month period from the International Institute for the Advancement of Medicine (IIAM). The average age of the male donors was 50 years (range 5-69) and the average age of the female donors was 45 years (range 13-74).

The causes of death were intracranial hemorrhage (n = 16 or 52%), motor vehicle accident (n = 7 or 23%), head trauma (n = 4 or 13%), brain tumor (n = 2 or 6%), drug overdose (n = 1 or 3%) and respiratory arrest (n = 1 or 3%). Both serum and liver tissue were obtained from 23 donors; 7 donors contributed liver tissue only and 1 donor contributed serum only. Serum samples were obtained from 5 mL of blood; liver samples consisted of 10 g of tissue. Samples were frozen at IIAM and shipped frozen to 3M for analysis. Samples were extracted using an ion-pairing extraction procedure and were quantitatively assayed using HPLC-ESMSMS and evaluated versus an unextracted curve. Extensive matrix spike studies were performed to evaluate the precision and accuracy of the extraction procedure.

Result : Serum values for PFOA ranged from < LOQ (<3.0) - 7.0 ng/mL. Assuming the midpoint value between zero and LOQ serum value for samples <LOQ, the mean serum PFOA level was 3.1 ng/mL with a geometric mean of 2.5 ng/mL. No liver to serum ratios were provided because more than 90% of the individual liver samples were <LOQ. Liver PFOS concentrations ranged from <4.5 ng/g (limit of quantitation, LOQ) to 57.0 ng/g. Serum PFOS concentrations ranged from <6.1 ng/mL (LOQ) to 58.3 ng/mL. Among the 23 paired samples, the mean liver-to-serum ratio was 1.3:1. This liver-to-serum ratio is comparable to that reported in a toxicological study of cynomolgus monkeys, which had liver and serum concentrations 2-3 orders of magnitude higher than observed in these human donors.

This information may be useful in human risk characterization for PFOS. Liver to serum ratios were not estimated for PFOA, PFHxS, and PFOSA, as 90% of the human donor liver samples were determined to have less than the LOQ.

Test substance : PFOA

08.12.2005 (477) (478)

Type of experience : Direct observation, other

Method : A screening study was undertaken to compare branched and linear isomers of PFOA in 4 lots of commercial pooled human sera with concentrations ranging from 0.65 to 5.6 ng/mL PFOA.

Result : Results from this study showed a wide distribution of the percentage of

branched isomers of PFOA compared to the linear isomer of PFOA in the commercial pooled populations (% branched/sum branched plus linear = <0.31, 16, 14, and <0.21). Two lots of the commercial pooled sera showed the presence of branched isomers of PFOA while the other two lots showed a much lower percentage (by at least 40x) of PFOA branched isomers.

Test substance : PFOA
08.12.2005 (16)

Type of experience : Direct observation, other

Method : A screening study of 3 lots of commercial pooled human plasma, one lot of pooled human plasma from central China, and four lots of commercial pooled human serum was undertaken to quantify endogenous levels of C7, C8, C9, C10, C11, C12 and PFOS.

Result : Results from this study showed quantifiable levels of the linear isomers of C7, C9-C12 ranging from <0.010-0.9 ng/mL. Low to non-detect levels of branched isomers were observed for the C7 and C9-C12 compounds detected. PFOS was present in the screened lots of the commercial sera and plasma in concentrations ranging from 2.5-27 ng/mL and was present as branched and linear isomers. PFOA was present in the screened lots of commercial sera and plasma in concentrations from 0.65-5.6 ng/mL and was present as branched and linear isomers.

Test substance : PFOA
08.12.2005 (15)

Type of experience : Direct observation, other

Method : 11 PFCs were measured in 23 pooled serum samples collected in the United States from 1990 through 2002, and in serum samples collected in 2003 from 44 residents from Trujillo, Peru.

Result : PFOS and PFOA were detected in all the pooled samples; perfluorohexane sulfonic acid (PFHxS) was detected in 21. Median concentrations were 31.1 ug/L (PFOS), 11.6 ug/L (PFOA), and 2 ug/L (PFHxS). The 90th percentile concentrations of PFCs in the 44 Peruvian residents were 0.7 ug/L (PFOS), 0.1 ug/L (PFOA), and <0.3 ug/L (PFHxS). The frequencies of detection were 20% (PFOS), 25% (PFOA), and 9% (PFHxS). The frequent detection of selected PFCs in the pooled samples from the United States and the lack of clear concentration trends based on a year of collection suggest a sustained widespread exposure to these compounds among US residents, at least since the 1990s. By contrast, the much lower frequency of detection and concentration ranges of PFCs in Peru suggest a lower exposure of Peruvians to PFCs compared with North Americans. Genetic variability, diet, lifestyle, or a combination of all these may contribute to the different patterns of human exposure to PFCs in the United States and Peru.

Test substance : PFOA
08.12.2005 (115)

Type of experience : Direct observation, other

Method : Concentrations and accumulation of 13 fluorinated organic compounds (FOCs) in human sera and seminal plasma were measured in an Asian developing country, Sri Lanka.

Result : Six of the FOCs, PFOS (perfluorooctanesulfonate), PFHS (perfluorohexanesulfonate), PFUnA (perfluoroundecanoic acid), PFDA (perfluorodecanoic acid), PFNA (perfluorononanoic acid) and PFOA, were detected in all of the sera samples. Measurable quantities of two main perfluorosulfonates, PFOS and PFHS, were found in all seminal plasma samples. The detection frequency of the predominant perfluoroalkylcarboxylate, PFOA, in seminal plasma was >70%. Accumulation of PFOS in sera was significantly positively correlated with

PFOA, PFHS and PFNA. Positive linear regressions were also found between PFNA and PFUnA and PFNA and PFDA suggesting that these compounds may have a similar origin of exposure and accumulation. Significantly positive associations were observed for partitioning of both PFOS and PFNA between sera and seminal plasma. The accumulation of FOCs was not significantly different in sera from Colombo (urban population) and Talawakele (rural conventional tea workers). However, the Haldummulla population (rural organic tea workers) had relatively lower exposure to FOCs compared to the other two groups, urban and rural conventional tea workers. Concentrations of FOCs in Sri Lanka were similar to those reported for industrialized countries suggesting that human exposure to such chemicals is widespread even in developing countries. The novel finding of FOCs in human seminal plasma implies that further studies are needed to determine whether long-term exposure in humans can result in reproductive impairments.

Test substance : PFOA

08.12.2005 (289)

Type of experience : Direct observation, other

Method : Inorganic and organic fluoride was measured in plasma samples from humans living in 5 cities.

Result : Almost all of the 106 human plasma samples contained measurable quantities of inorganic fluoride and organic fluorocompounds. The average fluoride concentration in plasma was directly related to the fluoride concentration in the water supply, but the average organic fluorine concentration was not. The organic fluorocompounds were purified from 20 L of pooled plasma and characterized by NMR. The organic fluorocompounds identified were C6-C8 fatty acid derivatives which accounted for one-third of the original organic fluorine content, indicating human plasma also contains other forms of organic fluorocompounds. The major fluorocarbon isolated resembled PFOA.

08.12.2005 (291)

Type of experience : Direct observation, other

Method : Individual blood samples from 3 different populations were recently analyzed for PFOA and other fluorochemicals. The studies' participants included adult blood donors, an elderly population participating in a prospective study in Seattle, WA, and children from 23 states participating in a clinical trial.

Through cooperation with six American Red Cross blood banks, 645 serum samples from adult donors (ages 20 69, equally represented of both sexes) were obtained for fluorochemical analyses. Blood bank locations were Los Angeles (CA), Portland (OR), Minneapolis St. Paul (MN), Charlotte (NC), Hagerstown (MD) and Boston (MA). Samples were void of personal identifiers. Age, gender and location were the only known demographic factors.

Sera samples were extracted and quantitatively analyzed for seven fluorochemicals using high pressure liquid chromatography/electrospray tandem mass spectrometry and evaluated versus an extracted curve from a human plasma matrix. The seven fluorochemicals were perfluorooctanesulfonate (PFOS); N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA); N-methyl perfluorooctanesulfonamidoacetate (M570); perfluorooctanesulfonamidoacetate (M556); perfluorooctanesulfonyl amide (PFOSA); PFOA; and perfluorohexanesulfonate (PFHS).

A total of 238 serum samples from elderly volunteers from a large prospective longitudinal study designed to examine cognitive function among male and female subjects, ages 65 to 96, in the Seattle (WA) area

were obtained for fluorochemical analyses. Samples were void of personal identifiers. The only known demographic factors were: age, gender and the number of years residence in Seattle.

Result : Overall, the PFOA means were similar across all 3 populations (4.6 ppb, 4.2 ppb, and 4.9 ppb, respectively). The geometric means and 95% tolerance limits (the proportion of the population expected to be found) and their upper bounds were comparable across all 3 studies. However, the upper ranges for the children and adults were much higher than for the elderly population. It is not clear whether this is the result of geographic differences in PFOA levels or some other factor. It should be noted that PFOS and PFOA were highly correlated in all three studies (r = 0.63, 0.70, and 0.75, respectively) and that PFOA did not meet the criteria for a log normal distribution based on the Shapiro-Wilk test in any of these studies.

Overall, the geometric mean measured concentration of PFOS was 34.9 ppb. The measured PFOS concentration ranged from less than the lower limit of quantitation (LLOQ) of 4.1 ppb to 1656.0 ppb. The geometric mean for PFOS was significantly higher among males (37.8 ppb) than females (31.3 ppb). No significant difference was observed with age. Charlotte (NC) had the highest geometric mean serum PFOS concentration (51.5 ppb) and Boston (MA) the lowest (29.5 ppb). Bootstrap analyses were used to calculate a 95% tolerance limit for PFOS of 88.5 ppb with an upper 95% confidence limit of 100.0 ppb.

Geometric mean data are reported for PFOA (4.6 ppb), PFHS (1.9 ppb), PFOSAA (2.0 ppb), and M570 (1.3 ppb). The geometric mean and 95% tolerance limits of these fluorochemicals were, on average, an order of magnitude (or more) lower than PFOS. PFOS and PFOA were highly correlated (r = .63). PFOS had lower correlations with PFOSAA (r = .42), PFHS (r = .38) and M570 (r = .20). The number of samples with measured PFOSA and M556 concentrations below the LLOQ prohibited meaningful statistical analyses for these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with those previously reported. The human data, to date, suggests the approximate average serum concentration in non-occupational adult populations may be 30 to 40 ppb with 95% of a population's serum PFOS concentrations below 100 ppb. Since serum PFOS concentrations likely reflect cumulative human exposure, this information will be useful for risk characterization (3M Data, 2002a).

Overall, the geometric mean measured concentration of PFOS was 31.0 ppb. The measured PFOS concentration ranged from less than the lower limit of quantitation (LLOQ) of 3.4 ppb to 175.0 ppb. There was no significant difference in the PFOS geometric means by sex or years residence in Seattle. Age was negatively associated with PFOS. Bootstrap analyses were used to calculate a 95% tolerance limit for PFOS of 84.1 ppb with an upper 95% confidence limit of 104.0 ppb. Geometric mean data are reported for PFOA (4.2 ppb), PFHS (2.2 ppb), PFOSAA (1.5 ppb), and M570 (1.2 ppb). The geometric means and tolerance limits for these fluorochemicals were, on average, an order of magnitude (or more) lower than PFOS. There was a strong correlation between PFOS and PFOA (r = .75), PFOS had lower correlations with PFOSAA and PFHS (r = .42), and lower yet with M570 (r = .29). The number of samples with measured concentrations of PFOSA and M556 below the LLOQ prohibited meaningful statistical analysis of these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with serum PFOS levels of the American Red Cross blood donors, ages 20 to 69. These and other data suggest the average serum concentration in the non occupational adult population data approximates 30 to 40 ppb with 95% of the population's serum PFOS concentrations

below 100 ppb. Since serum PFOS concentrations likely reflect cumulative human exposure, this information will be useful for risk characterization (3M Data, 2002b).

The purpose of this study was to better characterize the distribution of seven fluorochemicals, including perfluorooctanesulfonate (PFOS) in 599 pediatric samples obtained from a multi center clinical trial of group A streptococcal infections. Serum samples were collected in 1994 1995 and frozen at 20 C. The samples were void of personal identifiers. The only known demographic factors were: age (2-12), gender and the state residence (n = 23 states and the District of Columbia).

Overall, the geometric mean measured concentration of PFOS was 37.5 ppb. The measured PFOS concentrations ranged from 6.7 ppb to 515.0 ppb. Male children had a significantly higher geometric mean serum PFOS level compared to female children [male children geometric mean = 40.1 ppb vs. female geometric mean = 35.2 ppb. Bootstrap analysis was used to calculate a mean 95% tolerance limit of 88.5 ppb with an upper 95% confidence limit of 97.0 ppb. Additional geometric mean and tolerance limit data are reported for PFOA (4.9 ppb), PFHS, PFOSAA, and M570. A unique finding observed in these pediatric data that was not observed in the adult or elderly data reported elsewhere, were the higher 95% tolerance limit mean concentrations for PFHS (64.5 ppb) and M570 (11.9 ppb) with upper 95% confidence limits of 80.6 ppb and 14.8 ppb, respectively. It is unlikely that these findings are a consequence of analytical systematic error between these three studies. There was a strong correlation between PFOS and both PFOA (r = .70) and PFHS (r = .66) with lower correlations with PFOSAA (r = .43) and M570 (r = .42). The number of samples with measured concentrations of PFOSA and M556 less than the LLOQ prohibited meaningful statistical analyses for these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with serum PFOS levels of 645 American Red Cross blood donors (3M Data, 2002a) and 238 elderly subjects from a longitudinal study of cognitive function (3M Data, 2002b). Along with other human data, the average serum PFOS concentration in non-occupational human populations may approximate 30 to 40 ppb with 95% of the population's serum PFOS concentrations below 100 ppb. Since serum PFOS concentration likely reflects cumulative human exposure, this information will be useful for risk characterization. The higher mean 95% tolerance limits for PFHS and M570 suggest that some children may have had a greater exposure experience than adults and the elderly to products containing perfluorohexanesulfonyl fluoride (PHSE) and N-methyl perfluorooctanesulfonamidoethanol (N-MeFOSE) surface protectants (3M Data, 2002c).

08.12.2005 (17) (18) (19) (473) (474) (475)

Type of experience : other: Risk characterization

Method : PFOA, an environmentally and metabolically stable perfluorinated carboxylic acid, has been detected in the serum of children, adults and the elderly from the United States with the upper bound of the 95th percentile estimate in the range of 0.011-0.014 microg/mL (ppm). In this risk characterization, margins of exposure (MOE), which can provide a realistic perspective on potential for human risk, were determined by comparison of general population serum PFOA concentrations with serum concentrations from toxicological studies that are associated with the lower 95% confidence limit of a modeled 10 percent response or incidence level (LBMIC(10)) using USEPA BMDS software. The LBMIC(10) was estimated using surrogate data from other studies or pharmacokinetic relationships if serum PFOA data were not available.

Result : Modeled dose-responses (with resulting LBMIC(10) values) included post-natal effects in rats (29 microg/mL), liver-weight increase (23 microg/mL), and body-weight change (60 microg/mL) in rats and monkeys, and incidence of Leydig cell adenoma (125 microg/mL) in rats. MOE values based on the upper bound 95th percentile population serum PFOA concentration were large, ranging from 1600 (liver-weight increase) to 8900 (Leydig cell adenoma). These MOE values represent substantial protection of children, adults, and the elderly.

08.12.2005 (108)

Type of experience : other: Risk characterization

Method : Articles manufactured from fluoropolymers containing perfluorooctanoate (PFOA) and articles manufactured with fluorotelomer-based products which may contain PFOA as an unintended byproduct were evaluated either quantitatively or qualitatively. Specifically, hypothetical exposure estimates were calculated for mill-treated carpeting, carpet care solution, treated apparel, treated nonwoven medical garments, nonstick cookware, and thread seal tape.

Quantitative assessments based on potential PFOA concentrations and an evaluation of relative contact frequency were also performed for stone, tile and wood sealants; industrial floor waxes and removers; latex paint; home and office cleaning products; upholstery, home textiles, and technical textiles; and membranes for apparel.

Qualitative assessments were performed for those article groups where complete exposure pathways were not identified, or contact is considered to be negligible relative to other articles evaluated quantitatively. The article groups addressed qualitatively in this study are hose and tubing; cable and wire; and architectural fabrics.

The exposure assessment focuses on consumer use of these articles. In this study, consumers include both residents (at home, school, and work) and professionals (at their place of employment) who may come into contact with articles evaluated in the assessment. Thus, hypothetical levels of exposure are estimated for infants, children, adolescents, and adults using analytical data collected on PFO levels in the articles and conservative estimates of contact with the articles. Both Reasonable Maximum Exposure (RME) and More Typical Exposure (MTE) estimates are calculated, consistent with guidance issued by EPA. The risk characterization uses a Margin of Exposure (MOE) approach, based on these exposure estimates and Health Benchmarks derived from existing toxicity data and information on PFOA. Specifically, the MOE represents the ratio of a Health Benchmark to an exposure estimate.

Result : Based on all available toxicity and analytical data, exposures to PFOA in the consumer articles evaluated in this study are not expected to have the potential to cause adverse health effects in infants, children, adolescents, and adult residents or professionals, even in sensitive individuals within the general population. Specifically, the MOEs calculated in this evaluation range from approximately 30,000 to over one million under the RME scenarios, representing sizeable margins of exposure using conservative assumptions. MOEs for the MTE scenarios are even larger.

08.12.2005 (229) (624)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

Test substance : PFOA
Method : other

Method : A selective and sensitive method for analysis of PFOA in human serum and plasma, utilizing liquid chromatography tandem mass spectrometry (LC-MS/MS), has been developed and thoroughly validated to satisfy strict FDA guidelines for bioanalytical methods. A simple, automated sample preparation procedure, involving extraction of the target analyte with acetonitrile on protein precipitation media in a 96-well plate format was developed, allowing efficient handling of large numbers of samples. The proposed method uses the calibration standards prepared in a surrogate matrix (rabbit serum or plasma) and (13)C-labeled PFOA as the internal standard to account for matrix effects, instrument drift, and extraction efficiency. Human serum and plasma could not be used for matrix matching of calibration standards as endogenous levels of PFOA observed in the control human serum and plasma significantly exceeded the targeted lower limit of quantitation (LLOQ) of the method.

The results of the validation experiments comply with the precision and accuracy limits defined by the FDA guidance document: "Guidance for Industry, Bioanalytical Method Validation", May 2001.

Result : Precision and accuracy of the method were demonstrated by analysis of rabbit serum and plasma control samples fortified at 0.5, 5, and 40 ng/mL PFOA and human serum and plasma fortified at 1.0, 5.0, 40 ng/mL PFOA. The LLOQ of 0.5 ng/mL PFOA was experimentally demonstrated for rabbit and human serum and plasma. Within-day precision and accuracy, short-term stability, freeze-thaw stability, equivalence of response between PFOA and APFO (the ammonium salt of PFOA), and dilution of concentrated samples were also investigated.

08.12.2005 (263)

Test substance : PFOA
Method : other

Method : A method is described for determining fluorinated organic compounds such as perfluorooctane sulfonate (PFOS), PFOA and perfluorooctanesulfonylamide (PFOSA) in human blood samples by column-switching liquid chromatography-electrospray mass spectrometry. The sample preparation prior to solid phase extraction (Waters Oasis HLB extraction column) involved simply mixing plasma sample with internal standard followed by centrifugation and extraction. The compounds were separated by reversed-phase chromatography with a C(8) column, and detected by mass spectrometry using selected ion monitoring in the negative mode.

Result : The average recoveries of PFOS, PFOA and PFOSA ranged from 82.2 to 98.7% (R.S.D.: from 2.0 to 5.2%, n = 6). The limits of quantitation of PFOS, PFOA and PFOSA at signal to noise (S/N = 10) were 0.5, 0.5 and 1.0 ng/mL. The method enables the precise determination of standards and can be applied to the detection of PFOS, PFOA and PFOSA in human plasma samples for monitoring human exposure.

08.12.2005 (333)

Test substance : PFOA and PFOS
Method : other

Method : A method for the determination of perfluorooctanesulfonate (PFOS) and PFOA simultaneously with 10 closely related perfluorochemicals (PFCs) in

human whole blood was developed and validated. The main part of the data on PFCs in human blood is from serum samples, analyzed mainly by ion pair extraction followed by high-performance liquid chromatography (HPLC) and negative electrospray (ESI) tandem mass spectrometry (MS/MS). The analytical method developed here is suitable for human whole blood and involves solid-phase extraction (SPE) and HPLC negative electrospray single quadrupole mass spectrometry (HPLC/ES-MS). A whole blood aliquot was treated with formic acid and extracted on a octadecyl (C18) SPE column. The PFCs were isolated with methanol, and quantification was performed using single quadrupole mass spectrometry and perfluoroheptanoic acid as internal standard.

Result : Validation was performed in the range 0.3-194 ng/mL with recovery between 64 and 112% and limit of detection in the 0.1-0.5 ng/mL range for 11 of the 12 PFCs studied. This method was applied to 20 whole blood samples collected in 1997-2000 from the Swedish population in the ages 24-72. Eleven of the 12 PFCs were detected, and were quantitatively and qualitatively confirmed using triple quadrupole LC/MS/MS analysis. PFOS, perfluorooctanesulfonamide, perfluorohexanesulfonate, PFOA and perfluorononanoic acid were quantified in all samples. In addition, perfluorohexanoic acid, perfluorodecanoic acid, perfluorodecanesulfonate, perfluoroundecanoic acid, perfluorododecanoic acid, and perfluorotetradecanoic acid were detected in some samples. This study shows that SPE and single quadrupole MS can be applied for extraction and quantification of PFCs in human whole blood, resulting in selectivity and low detection limits.

08.12.2005 (354)

Test substance : PFOA
Method : other

Method : Both pressurized solvent extraction (PSE) and reflux extraction in various solvents were used to select the most efficient system for the determination of the quantity of PFOA present in polytetrafluoroethylene polymers. After evaporating the solvent, PFOA was determined using liquid chromatography tandem mass spectrometry.

Result : PFOA concentrations were determined to be 140 ppb and 158 ppb in the PTFE polymers. Pressurized solvent extraction resulted in greater PFOA extraction then reflux. Recovery of spike standards were greater with water, ethanol and methanol (>89%). Acetonitrile recovery was poor (<8%).

29.12.2006 (404)

Test substance : PFOA
Method : other

Method : Methods were developed to quantify the amount of PFOA extracted from textile and carpet samples through contact with water, methanol, and sweat and saliva simulants using LC/MS/MS. The limit of quantitation (LOQ) for samples extracted in water and sweat simulant is 1 ppb (ng PFOA/g) while the limits of quantitation for samples extracted in saliva simulant and methanol were 3 ppb and 2.5 ppb, respectively.

Result : Method validation results are provided for a polyester control textile sample that was extracted in water on two different days by different analysts, which gave an overall recovery of 103% and standard deviation of 5.3% for 30 analyses. However, for routine application of these methods to a large number of sample sets differing in chemical and physical compositions, a complete validation for each sample type is not practical or possible since control samples for fortifications are often not available. Instead, suitable analytical methods and acceptance criteria are described which ensure accurate PFOA quantitation in each of the solvent extract types. During routine use of these methods, post-extraction spike recoveries for the different sample types and solvents are 100 +/- 15% using a dual

isotopically labeled (13)C-PFOA internal standard to correct for matrix effects. A comparison of extraction solvent versus time using a wrist action shaker for textile and carpet samples demonstrates that the total extractable amount of PFOA is similar for each of the solvent types. However, as expected the rate of extraction in water and simulants is significantly less than that of methanol. Finally, a comparison of 2 hour and 24 hour wrist action shaker extractions with a 1.5 hour pressurized fluid extraction (PFE) in methanol reveals that the 24 hour wrist action shaker yields the highest results. The 2 hour wrist action shaker results are similar to those of the 1.5 hour PFE extraction.

08.12.2005 (435)

Test substance : PFOA
Method : other

Method : This study reports on the development and validation of a method for the determination of PFOA in air samples. This method uses the OSHA Versatile Sampler (OVS) with a nominal 0.3 um filter and polystyrene resin sorbent (XAD-2 or XAD-4) followed by determination of PFOA by liquid chromatography mass spectrometry.

Result : The method was validated in the range of 0.474 to 47.4 ug/m3 for a 480-L sample. Breakthrough studies showed samples could be collected at I L/min for 24 hours or at 15 L/min for up to 8 hours without breakthrough. Extract storage stability tests showed that sample extracts in methanol remain stable in glass autosampler vials for up to 13 days following initial injection. PFOA stability on OVS tubes was unaffected at both refrigerated and ambient temperatures. The overall average retention efficiency was 92.1% with a pooled RSD95 of 5.8% at five concentration levels (0.474 ug/m3 to 47.4 ug/m3).

08.12.2005 (345)

Test substance : PFOA
Method : other

Method : A high-throughput method was developed for measuring trace levels of 13 PFCs (2 perfluorosulfonates, 8 perfluorocarboxylates, and 3 perfluorosulfonamides) in serum and milk using an automated solid-phase extraction (SPE) cleanup followed by HPLC-tandem mass spectrometry. The method is sensitive, with limits of detection between 0.1 and 1 ng in 1 mL of serum or milk, is not labor intensive, involves minimal manual sample preparation, and uses a commercially available automated SPE system. The method is suitable for large epidemiological studies to assess exposure to PFCs.

Result : The serum levels of these 13 PFCs were measured in 20 adults non-occupationally exposed to these compounds. Nine of the PFCs were detected in at least 75% of the subjects. Perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHxS), 2-(N-methyl-perfluorooctanesulfonamido) acetate (Me-PFOSA-AcOH), PFOA, and perfluorononanoate (PFNA) were found in all of the samples. The concentration order and measured levels of PFOS, PFOA, Me-PFOSA-AcOH, and PFHxS compared well with human serum levels previously reported. Although no human data are available for the perfluorocarboxylates (except PFOA), the high frequency of detection of PFNA and other carboxylates in the authors' study suggests that human exposure to long-alkyl-chain perfluorocarboxylates may be widespread. The authors also found PFOS in the serum and milk of rats administered PFOS by gavage, but not in the milk of rats not dosed with PFOS. Furthermore, the authors did not detect most PFCs in two human milk samples. These findings suggest that PFCs may not be as prevalent in human milk as they are in serum.

08.12.2005 (398)

Test substance : Total Fluorine
Method : other

Method : The difficulty in determining fluorine in organic substances is primarily in the data interpretation since very energetic agents must be used to destroy the carbon fluorine bond. Development of the oxy-hydrogen torch combustion system allowed the determination of fluorine-containing compounds, in some cases, to levels as low as the 20 mg/kg level. In this method, however, only total fluorine is determined and no speciation is possible.

15.11.2005 (626)

Test substance : Fluorine in human blood serum
Method : other

Method : The level of fluorine in human blood serum was determined by comparing the levels in ashed and unashed samples to demonstrate that there were two forms of fluorine in blood, "exchangeable and non-exchangeable". The latter might be organically-bound fluorine.

08.12.2005 (591)

Test substance : PFOA in blood and other biological samples
Method : other

Method : A gas chromatographic method was developed to determine PFOA in blood and other biological samples. The method required the use of diazomethane to form the methyl ester of PFOA. The method was able to measure PFOA levels as low as 15 ug/L.

08.12.2005 (84) (85)

Test substance : PFOA in groundwater
Method : other

Method : To measure PFOA in groundwater, a GC/MS method was used. With this method, a limit of quantitation (LOQ) of 36 ppb and a limit of detection (LOD) of 18 ppb [LOD = 18 ppb; LOQ = 36 ppb; Concentration Factor = 55-200; Calibration range = 3.6-1080 ug; and Spike recovery = 73-90%] were obtained.

26.10.2005 (443)

Test substance : Fluorotelomer carboxylic acids in rainwater
Method : other

Method : A method based on LC/MS/MS analysis of fluorotelomer carboxylic acids (FTCAs: CnF2n+1CH2COOH, n = 6, 8, and 10) and fluorotelomer unsaturated carboxylic acids (FTUCAs: CnF2nCHCOOH, n = 6, 8, and 10) in rainwater using negative ionization electrospray multiple reaction monitoring conditions is described. Preconcentration from rainwater samples was achieved using solid-phase extraction on C18 sorbent. Low parts per trillion levels of the C10- and C12-FTCAs and FTUCAs were detected, suggesting that one possible pathway of removing FTOHs from the atmosphere is through oxidation and wet deposition.

Result : Perfluorocarboxylic acids (PFCAs) and perfluorooctane sulfonate (PFOS) were simultaneously analyzed in the rainwater samples using established LC/MS/MS methods [LOD = 7.2 ppt; LOQ = 1 ppb; Concentration Factor = 4000; Calibration range = 1-50 ppb; Spike recovery = Not detected].

25.10.2005 (420)

Test substance : PFOA in seawater
Method : other

Method : Sources of procedural and instrumental blank contamination by

perfluorinated acids have been identified and eliminated, to reduce background levels in blanks and thereby improve limits of quantitation. This method is capable of detecting perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS), perfluorobutanesulfonate (PFBS), PFOA, perfluorononanoate (PFNA), and perfluorooctanesulfonamide (PFOSA) at low pg/L levels in oceanic waters [LOD = 5.2 pg/L (ppq); LOQ = Not reported; Concentration Factor = 2000-5000; Calibration range = 1-500 ppt; Spike recovery = 124% (C18)].

08.12.2005 (639)

Test substance : PFOA in seawater
Method : other

Method : A solid-phase extraction procedure coupled with high-performance liquid chromatography interfaced to high-resolution mass spectrometry was used to isolate, identify, and quantify small concentrations of PFCs in seawater [LOD = Not reported; LOQ = 0.02 ppt; Concentration Factor = 400-2500; Calibration range = 0.02 pg/mL (upper level not reported); Spike recovery = 170%].

15.11.2005 (566)

Test substance : PFOA in surface water
Method : other

Method : PFOA concentrations in surface water were analyzed by LC/MS with a solid phase extraction method [LOD = 0.06 ppt; LOQ = 0.1 ppt; Concentration Factor = 1000; Calibration range = 0-2 ppt and 5-150 ppt; Spike recovery = 92-99%].

26.10.2005 (535)

Test substance : PFOA in surface water
Method : other

Method : Two analytical methods for the determination of perfluorinated surfactants in aqueous samples were developed. With the first method, aliquots of surface water (0.2-200 mL) were preconcentrated using solid-phase extraction. Liquid chromatography/tandem mass spectrometry was employed for identification and quantification of each perfluorinated surfactant. A second method employing 19F NMR was developed for the determination of total perfluorinated surfactant concentrations in aqueous samples (2-100 mL) [LOD = 1 pg; LOQ = 9 ppt; Concentration Factor = 100; Calibration range = 0.46-325 ppb; Spike recovery = 80-100%].

25.10.2005 (445)

Test substance : PFOA in river water
Method : other

Method : A solid-phase extraction method coupled with HPLC-negative- ion electrospray tandem mass spectrometry was developed to quantitatively measure trace levels of organic fluorochemicals in drinking water and surface water. Using this method, certain fluorochemicals can be quantitatively measured in water samples down to 25 ppt, a level well below calculated drinking water advisory levels [LOD = 5 ng/L; LOQ = 10-25 ng/L; Concentration Factor = 8; Calibration range = 10-5000 ng/L; Spike recovery = 112%].

15.11.2005 (303)

Test substance : PFOA in lake water
Method : other

Method : The monitored perfluorooctane surfactants were quantitatively determined using single quadrupole HPLC/MS and qualitatively confirmed using ion

trap MS/MS. Additionally, PFOS was quantitatively confirmed using triple quadrupole LC/MS/MS [LOD = 6 pg/mL; LOQ = 13 pg/mL; Concentration Factor = 2500; Calibration range = 1-500 ng/L; Spike recovery = 109%].

25.10.2005 (104)

Test substance : PFOA in water
Method : other

Method : A method was developed for the trace level analysis of C8, C9, C10, C11, and C13 perfluorocarbon carboxylic acids in water. Samples were concentrated by solid-phase extraction (SPE) before analysis by combined liquid chromatography/electrospray tandem mass spectrometry (LC/MS/MS). A surrogate standard, 9-hydrohexadecafluorononanoic acid (9H), was used to monitor recovery.

Result : The lower limit of quantitation (LLOQ) for C8, C9, C10, C11, and C13 was determined to be 25 ng/L in water. The specificity of the method was established by showing no significant interferences (<20% of the LLOQ standard) in control samples of well, stream, spring, tap, omnisolve, and type I water at the retention time of the target analytes. The linearity of the method was determined; the coefficients of determination for the five calibration curves generated were all >0.985. Good within-day and between-day accuracy and precision were demonstrated. Extracts and standards were shown to be stable after remaining at room temperature for ~ 24 hours. Samples fortified with C8, C9, C10, and C11 were shown to be stable after remaining at room temperature for 14 days before extraction. Samples fortified with C13 were shown to be stable after remaining at room temperature for 7 days before extraction. Fortified samples, extracts, and standards demonstrated stability after being stored in a refrigerator for 14 days for all analytes. Long-term storage stability was demonstrated for methanolic stock solutions [LOD = Not reported; LOQ = 25 ppt; Concentration Factor = 8; Calibration range = 25-1000 ppt; Spike recovery = Not reported].

08.12.2005 (526)

Test substance : Perfluorocarboxylic acids in water
Method : other

Method : A rapid, selective and simple analytical procedure using tetrabutylammonium as ion pair in conjunction with solid-phase microextraction followed by in-port derivatization-GC-negative ion chemical ionization mass spectrometry was developed. The procedure allows an accurate determination of perfluoroalkylcarboxylic acids in aqueous samples at ng/L levels (i.e. method detection limit 20 ng/L for perfluorodecanoic acid) improving previous GC methods in terms of analysis time and sensitivity. Ammonia as reagent gas in the negative ion chemical ionization mass spectrometry increased the sensitivity at least 3-fold compared to methane for perfluorocarboxylic acid butyl esters.

Result : The developed procedure was successfully applied to effluents from wastewater treatment plants (i.e. 0.05-8.2 ug/L) and harbor seawaters [LOD = 0.1 ug/L; LOQ = 0.34 ug/L; Concentration Factor = solid-phase microextraction; Calibration range = 0.035-150 ug/L; Spike recovery = 73-90%].

15.11.2005 (73)

Test substance : PFOA in lake water
Method : other

Method : A method was developed using the Oasis HLB solid phase cartridge to achieve the required method detection limits.

Result : PFOS and PFOA concentrations were measured in surface waters collected from Michigan and New York [LOD = 8 ng/L; LOQ = 25 ng/L; Concentration Factor = 50; Calibration range = Not reported; Spike

recovery = Not reported].

26.10.2005 (556)

Test substance : PFOA in sea water
Method : other

Method : Water samples were collected in 10 L glass bowls The water was acidified with 10 mL of hydrochloric acid (25 %) to a pH of 2 to 3, and a solution of deuterated internal standards (d6-diuron and d3-mecoprop) is added. 9 L of this sample are pumped over a cartridge filled with 4 g of Chromabond HR-P resin. After washing with pure water and drying in a stream of nitrogen, the cartridges are eluted with 100 mL of methanol in the reversed direction. After concentrating the extract to 200 µL(rotary evaporator, then N2-stream) 8 µL of this solution are injected into the HPLC-MS-MS system. (Agilent 1100 Series autosampler, binary pump, column oven (23°C) and Applied Biosystems API 2000 LC-MS-MS system. A Synergi Hydro-RP phase column is used. Eluent A consists of water with 10 mM ammonium acetate and 10 mM acetic acid, pH 4.5, eluent B is methanol with the same concentrations of buffering compounds. The mass spectrometric determination is carried out by negative electrospray ionisation in the multi reaction mode. The precursor ions are always the (M-1)- ions; for the sulfonic acids the fragmentation to the SO3- ion is observed, while for carboxylic acids the loss of CO2 is monitored [LOD = Not reported; LOQ = 0.05-0.5 ng/L; Concentration Factor = 45,000; Calibration range = Not reported; Spike recovery = Not reported].

15.11.2005 (117)

Test substance : PFOA in rain, sea, and lake water and in effluents
Method : other

Method : An HPLC system (1100 series, Agilent) in combination with a time-of-flight (TOF) mass spectrometer (LCT, Micromass) was used for quantification of all abiotic samples. Separation was performed on an ACE C18 column (150 x 2.1 mm, 3 mm particle size; ACT) employing a gradient of 200 uL/min 2 mM ammonium acetate in methanol and water. Electrospray ionisation in the negative ion mode was used applying the following parameters: Cone voltage -35 V; cone gas 10 L/h; desolvation gas 400 L/h. Mass spectra were recorded in full scan mode and for quantification extracted high resolution mass chromatograms were used [LOD = Not reported; LOQ = Not reported; Concentration Factor = Not reported; Calibration range = Not reported; Spike recovery = Not reported].

26.10.2005 (88)

Test substance : PFOA in air
Method : other

Result : PFOA was measured in airborne dust collected on quartz membrane filters near two Japanese cities. Although no data were available for the blank concentrations, PFOA levels were reported to be significantly higher than the blanks. No particle size speciation was performed [spike recovery was 89.4%].

25.10.2005 (308)

Test substance : Organofluorochemicals in air
Method : other

Method : Techniques were evaluated for the determination of 19 organofluorochemicals and for total fluorine in ambient air samples. Due to the potential biphasic nature of most of these fluorochemicals when airborne, OSHA versatile sampler (OVS) tubes were used to simultaneously trap fluorochemical particulates and vapors from workplace air. Analytical methods were developed for OVS air samples to

quantitatively analyze for total fluorine using oxygen bomb combustion/ion selective electrode and for 17 organofluorochemicals using LC/MS and gas chromatography/mass spectrometry (GC/MS). The experimental design for this validation was based on NIOSH Guidelines for Air Sampling and Analytical Method Development and Evaluation, with some revisions of the experimental design. The study design incorporated experiments to determine analytical recovery and stability, sampler capacity, the effect of some environmental parameters on recoveries, storage stability, limits of detection, precision, and accuracy. Fluorochemical mixtures were spiked onto each OVS tube over a range of 0.06-6 ug for each of 12 compounds analyzed by LC/MS and 0.3-30 ug for 5 compounds analyzed by GC/MS. These ranges allowed reliable quantitation at 0.001-0.1 mg/m3 in general for LC/MS analytes and 0.005-0.5 mg/m3 for GC/MS analytes when 60 L of air are sampled. The organofluorochemical exposure guideline (EG) is currently 0.1 mg/m3 for many analytes, with one exception being APFO (EG is 0.01 mg/m3) Total fluorine results may be used to determine if the individual compounds quantified provide a suitable mass balance of total airborne organofluorochemicals based on known fluorine content. Improvements in precision and/or recovery as well as some additional testing would be needed to meet all NIOSH validation criteria This study provided valuable information about the accuracy of this method for organofluorochemical exposure assessment.

08.12.2005 (506)

Test substance : Perfluorocarboxylic acids
Method : other

Method : A capillary electrophoretic method with UV detection for separation and quantitation of perfluorocarboxylic acids (PFCAs) from C6-PFCA to C12-PFCA has been developed. The optimization of measurement conditions included the choice of the most appropriate type and concentration of buffer in the background electrolyte (BGE), as well as the type and the content of an organic modifier. The optimal separation of investigated PFCAs was achieved with 50 mM phosphate buffer and 40% isopropanol in the BGE using direct UV detection. The optimum wavelength for direct UV detection was optimized at 190 nm. For indirect detection, several chromophores were studied. Five mM 3,5-dinitrobenzoic acid (3,5-DNBA) in 20 mM phosphate buffer BGE and indirect UV detection at 280 nm gave the optimal detection and separation performance for the investigated PFCAs. The possibility of on-line preconcentration of solutes by stacking has been examined for indirect detection. The detection limits (LODs) determined for direct UV detection ranged from 2 ug/mL for C6-PFCA to 33 ug/mL for C12-PFCA. The LODs obtained for indirect UV detection were comparable to those obtained for direct UV detection.

15.11.2005 (633)

Test substance : Fluorochemicals in biological matricies
Method : other

Method : The compound-specific method for the extraction of extremely low levels of several commercial organic fluorochemicals from sera and liver with quantitative detection by negative ion electrospray tandem mass spectrometry described represents a robust, previously undescribed approach to quantifying specific organic fluorochemicals in biological matrices.

25.10.2005 (302)

Test substance : PFOA in biological samples
Method : other

Method : A method is described for the quantitative determination of perfluorinated carboxylic acids (PFCAs), perfluorohexanoic acid (C6-PFCA),

perfluoroheptanoic acid (C7-PFCA), perfluorooctanoic acid (C8-PFCA), perfluorononanoic acid (C9-PFCA) and perfluorodecanoic acid (C10-PFCA), in biological samples. PFCA in liver homogenates was extracted as an ion pair with tetrabutylammonium (TBA) ion into organic solvent, then the PFCA was derivatized with 3-bromoacetyl-7-methoxycoumarin (BrAMC) and quantified by HPLC with fluorescence detection. This method is applicable for the studies on tissue accumulation and elimination of PFCAs in animals after the administration.

25.10.2005 (464)

Test substance : PFOA in biological tissues
Method : other

Method : A method for the determination of tissue perfluorocarboxylic acids (PFCA) was developed using gas-liquid chromatography with an electron capture detector (ECD). PFOA, perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were efficiently extracted from rat liver, methylated with diazomethane, and separated on GLC. Internal standards that were added to liver homogenates were used in the quantitative analysis of PFCAs to correct the loss during the extraction and derivatization.

08.12.2005 (392)

Test substance : Fluorinated Organics in Air
Method : other

Method : A suite of potential PFOS precursors (sulfonamides) and fluorotelomer alcohols (FTOHs) were separated by gas chromatography and detected by chemical ionization mass spectrometry (GC/CI-MS). Full-scan spectra were collected in both positive and negative chemical ionization (PCI and NCI, respectively) mode to determine retention time windows and fragmentation patterns. In selected ion monitoring (SIM) mode, instrumental detection limits ranged from 0.2 to 20 pg for individual analytes, depending on ionization mode. PCI mode was preferred for routine analysis because of the simple mass spectra produced, typified by the presence of a major molecular ion [M + H]+. High-volume air samplers collected gaseous and particle-bound fluoroorganics on composite media consisting of XAD-2, polyurethane foam (PUF), and quartz-fiber filters. The combined collection efficiency for individual analytes was 87 to 136% in breakthrough experiments. Application of the method to the analysis of ambient air from urban and rural sites confirmed the presence of six novel fluorinated atmospheric contaminants at pg/m3 concentrations. Low concentrations of fluoroorganics were consistently detected in blanks (<4 pg/m3); however, this did not prevent confirmation or quantification of environmental concentrations.

25.10.2005 (431)

Test substance : PFOA
Method : other

Method : A procedure for the extraction, separation, and isolation of perfluorodecanoic and perfluorooctanoic acids from biological samples is described.

Result : The use of conventional lipid extraction procedures leads to substantial loss of the perfluorinated fatty acids added to tissue. The presence of sulfuric acid in aqueous saline during phase partitioning is essential for the recovery of perfluorodecanoic and perfluorooctanoic acids in the organic phase following their extraction from tissue. The perfluorinated fatty acids are co-eluted with simple lipids from silica gel columns using diethyl ether/trifluoroacetic acid (100:1, v/v). Simple lipids are separated by thin layer chromatography. By substituting trifluoroacetic acid for acetic acid in the developing solvents, perfluorodecanoic and perfluorooctanoic acids

migrate with other free fatty acids.

01.11.2005 (616) (617) (618)

Test substance : PFOA
Method : other

Method : A method of chromatographic analysis of PFOA was reported. Derivatives of PFOA and perfluorononanoic acid (PFNA) were prepared by the extractive alkylation procedure. To a mixture of dog plasma and 100 uL of perfluorononanoic acid (PFNA) were added 1 milliliter (mL) of tetrabutylammonium hydroxide (TBA) and 2 mL of buffer solution, followed by 5 mL of an ethyl acetate solution of 0.2 mL benzyl bromide. After sonification, the organic phase was separated and evaporated to dryness under nitrogen and dissolved in methylene chloride. PFNA, TBA, and buffer were added to dog urine, which was then extracted with diethyl ether. The residue from ether evaporation was dissolved in acetone and 0.1 mL of benzyl bromide was added. The contents were heated to 80°C, cooled, evaporated, and dissolved in methylene chloride. The product was analyzed by gas chromatography using fused silica capillary column and flame ionization detector. The benzyl esters of PFOA and PFNA eluted at 90 and 100°C, respectively. The derivatization reaction was verified by gas chromatography mass spectrometry analysis using electron impact ionization at 70 electron volts.

Result : Typical precision values in the determination of 5 ug/mL of PFOA in plasma and urine were 3.3 and 3.0 percent, respectively. The detection limit was 1 nanogram.

08.12.2005 (649)

Test substance : PFOA
Method : other: Quantitative screening on serum and plasma for determination of PFOA and other fluorinated compounds

Method : A quantitative screening method was described for the determination of a number of perfluorinated chemicals, including PFOS and PFOA, in human serum, human plasma, and monkey serum samples. Following an extraction procedure, samples were analyzed using electrospray LC/MS/MS.

Result : The quantitative screening of 64 serum and plasma samples produced levels of certain analytes at extremely low levels (< 100 ppt).

28.10.2005 (258)

Test substance : PFOS and PFOA
Method : other: Determination of PFOS, PFOA, and other fluorochemicals in animals.

Method : Serum and liver samples from fish, birds, and mammals were extracted and PFOS or other fluorochemical compounds were analyzed using HPLC-Electrospray mass spectrometry.

28.10.2005 (58)

Test substance : APFO
Method : other: Quantitative determination of APFO in human serum.

Method : Human serum samples were extracted by a liquid-liquid extraction procedure to isolate PFOA. Following reconstitution, sample extracts were analyzed by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the negative ion mode.

Result : All samples were successfully analyzed within one run. The lower limit of quantitation was 0.05 ug/mL for PFOA. The precision of four assays, as determined from the analysis of quality control samples for PFOA, were equal to or less than 7.78%, 8.93%, 8.23%, and 4.11%. The acceptance criteria for the quality control samples stipulated that two-thirds of the

individual samples must be within 15% of the nominal concentration.

15.11.2005 (69)

Test substance : PFOA
Method : A direct-injection, liquid-chromatography tandem mass spectrometry (LC MS/MS) method was developed.

Method : A direct-injection, liquid-chromatography tandem mass spectrometry (LC MS/MS) method was developed to quantify a suite of fluorotelomer sulfonate surfactants in groundwater collected from military bases where fire-training activities were conducted. The 4:2, 6:2, and 8:2 fluorotelomer sulfonates were detected and quantified in groundwater from two of the three military bases.
Result : The total fluorotelomer sulfonate concentrations observed at Wurtsmith AFB, MI, and Tyndall AFB, FL, ranged respectively from below quantitation (equal to or less than 0.60) to 182 ug/L and from 1100 to 14,600 ug/L, respectively. Analyses of a fluorotelomer-based AFFF concentrate by negative ion fast atom bombardment/mass spectrometry and LC MS/MS analyses indicate that the AFFF concentrate contains only a small amount of fluorotelomer sulfonates and that fluoroalkylthioamido sulfonates are the main anionic fluorosurfactant in the mixtures. PFOA concentrations ranged from below quantitation up to 6570 ug/L (these concentrations were determined by Moody and Field, 1999).

15.11.2005 (544)

Test substance : Organic fluorine compounds
Method : other

Method : Recovery of organic fluorine by direct aluminum monofluoride molecular absorption spectrophotometry, following injection of samples into the graphite furnace and use of sodium fluoride standards, varies from 0 to 100% from compound to compound depending on the compound's volatility and the mechanism of thermal decomposition. This problem has now been overcome by employing standards made from the very same fluorochemical that is present in the sample. This approach is applicable to samples containing only 1 known fluorochemical. Some industrial applications of this technique that meet the needs of quality control, industrial hygiene policies, and certain U.S. Food and Drug Administration regulations are described.

01.11.2005 (619)

Test substance : PFOA
Method : other

Method : A screening method for analysis of perfluoroalkylated substances (PFAS) in biota samples has been developed and validated using liver samples from polar cod (Boreogadus saida) and glaucous gull (Larus hyperboreus). The method was based on extraction of target compounds from homogenised samples into the solvent mixture used as mobile phase in high-performance liquid chromatography (HPLC), i.e. methanol/water (50:50; 2 mM ammonium acetate). The extract was filtered and directly injected into a HPLC/time-of-flight mass spectrometry (TOF-MS) system. Quantification was performed using 7H-perfluoroheptanoic acid as internal standard and a calibration standard solution dissolved in sample extract for each matrix type (matrix-matched calibration standard). The method is very time and cost efficient. Except for long-chain compounds and perfluorooctane sulfonamide (which cannot be covered by this method), recoveries were between 60% and 115% and method detection limits were in the range 0.04-1.3 ng/g wet weight. Blank values could be neglected with the exception of perfluorooctanesulfonate (PFOS), perfluorohexanoic acid (PFHxA) and PFOA. One of the major challenges in PFAS analysis is ionisation disturbance by co-eluting matrix in the ion source of the mass

spectrometer. Both matrix and analyte specific signal enhancement and suppression was observed and quantified. Repeated extractions (n = 3) gave relative standard deviations (RSD) <35% for all PFAS. Accuracy was examined by comparing the screening method to the generally applied ion pair extraction (IPE) method.

Result : PFAS concentration values of a glaucous gull liver sample deviated by less than 30% for the two methods, provided that matrix-matched calibration standards were employed in both methods.

08.12.2005 (86)

Test substance : PFOA
Method : other

Method : Salts of PFOA are polymerization aids used in the manufacture of fluoropolymers; one of the applications of fluoropolymers is the coating of metal cookware products. A method was developed to determine if PFOA might be present in and extracted from the surface of commercial frying pans coated with a DuPont fluoropolymer under simulated cooking conditions. Commercial grade cookware was obtained, then extracted with water and ethanol/water mixtures at 100 and 125°C, and the resulting extracts were analyzed by liquid chromatography tandem mass spectrometry (LC/MS/MS). Detection and quantification limits as low as 100 pg/cm2 were demonstrated.

Result : None of the fluoropolymer treated cookware samples analyzed showed detectable levels of PFOA when extracted under simulated cooking conditions.

08.12.2005 (502)

Test substance : PFOA
Method : other

Method : A method for the quantitative determination of PFOA in plasma by gas chromatography-electron capture detector is described. An HP-1 capillary column (30 m x 0.25 mm i.d. x 0.25 micron) was used. PFDA as the internal standard was added to a plasma sample, which was then lyophilized. The acids were derivatized to their methyl esters and then extracted into hexane.

Result : The calibration curve was linear over a range from 20.00 ug/L to 4000 ug/L with a correlation coefficient of 0.9946. The average recovery was 99.2% and the RSD was 0.95%. The detection limit was 6.0 ug/L. The level of PFOA in plasma of occupational workers was measured. The results showed that this method is accurate and reliable.

08.12.2005 (646)

Test substance : PFOA
Method : other

Method : A sensitive, specific, accurate and reproducible analytical method was developed and validated to quantify PFOA in human serum. After initial extraction with an ion-paring reagent, the procedure for quantifying PFOA is based on high-performance liquid chromatography (HPLC) interfaced to negative ion tandem mass spectrometry, operating in selected ion monitoring mode.

Result : The retention times of PFOA and its internal standard (D,L-malic acid) were 5.85 and 1.70 min, respectively. The assay was linear over the range 0-500 ng/mL, with a lower limit of quantification (LOQ) of 25 ng/mL, and with a coefficient of variation (CV) of 7.3%. The lower limit of detection (LOD) was assessed as 10 ng/mL. The overall precision and accuracy were assessed on 3 different days. The within- and between-day precision was 9.7 and 6.8%, respectively, and the accuracy was in the range 96-114%. The mean extracted recovery assessed at 3 different concentrations (100, 250, and 500 ng/mL) was always more than 85%. With this method no derivation

procedure was needed, thus avoiding possible thermal and chemical decomposition reactions of PFOA.

The assay was applied to quantify PFOA in serum from employees exposed to fluorochemicals commonly used in industrial applications for polymer production. The quantitative results for PFOA blood levels were found to range between 100 and 982 ng/mL.

08.12.2005 (574)

Test substance : PFOA
Method : other

Method : A reduced pressure helium microwave plasma detector was interfaced with a capillary gas chromatograph utilizing a dual capillary column system resulting in parallel detection using flame ionization (FID) or electron capture (ECD) and microwave emission. The system resulted in minimum loss of column resolution with the microwave emission detector (MED) and simultaneous data acquisition using eight element-specific channels with CRT and/or hard copy output. This system was applied to the detection and quantification of PFOA in human blood plasma resulting from an industrial exposure to this compound. This selective MED-fluorine channel greatly simplifies the interpretation of complicated FID and ECD capillary chromatograms and allows for straight-forward quantitation of perfluorooctanoate. The dual capillary MED was also utilized to characterize the fluorine containing metabolites in the plasma of rats which had been dosed with 1H,1H,2H,2H-perfluorodecanol. Five fluorinated compounds were observed, including perfluorooctanoate, the final metabolism product. Several of the metabolic intermediates were also identified.

08.12.2005 (292)

Test substance : PFOA
Method : other

Method : A rapid and sensitive method was developed for measuring 15 perfluorinated chemicals, including PFOS and PFOA, in breast milk and serum using high-performance liquid chromatography-tandem mass spectrometry. This method was used to measure the levels of perfluorochemicals in PFOS-dosed rats and in people non-occupationally exposed to these compounds.

Result : Stored samples of breast milk and serum from a 3M cross-fostering study in rats were analyzed. PFOS serum concentrations were significantly higher than in 8 control rats (80 ng/mL). Similarly, significant amounts of PFOS were found in the breast milk samples from 2 PFOS-dosed dams. No PFOS was detected in breast milk samples of the control rats.

This method was also used to measure the levels of perfluorochemicals in pooled serum samples from non-occupationally exposed people. Several perfluorochemicals were found at concentrations above the limit of detection (0.5 ng/mL). PFOS was found at the highest level (25.3 ng/mL), followed by PFOA (7.9 ng/mL), Et-PFOSA-AcOH (4.0 ng/mL), PFOSA (2.2 ng/mL), PFHxS (1.9 ng/mL), PFNA (1.3 ng/mL), and PFUA (1.6 ng/mL).

08.12.2005 (114)

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

Memo : Possibility of destruction: incineration

Method : The kinetics of the thermal decomposition of APFO was studied by high-temperature gas-phase nuclear magnetic resonance spectroscopy over the temperature range 196-234°C.

Result : APFO cleanly decomposes by first-order kinetics to give the hydrofluorocarbon 1-H-perfluoroheptane and is completely decomposed (>99%) in a matter of minutes at the upper limit of this temperature range. Based on the temperature dependence of the measured rate constants, we find that the enthalpy and entropy of activation are DeltaH++ = 150 +/- 11 kJ mol/l and DeltaS++ = 3 +/- 23 J mol/l/deg. These activation parameters may be used to calculate the rate of APFO decomposition at the elevated temperatures (350-400°C) at which fluoropolymers are processed; for example, at 350°C the half-life for APFO is estimated to be less than 0.2 seconds. These studies provide the fundamental parameters involved in the decomposition of the ammonium salt of perfluorooctanoic acid and indicate the utility of gas-phase NMR for thermolysis studies of a variety of materials that release compounds that are volatile at the temperature of decomposition and that contain an NMR-active nucleus.

08.12.2005 (386)

Memo : Possibility of destruction: incineration

Method : This study investigates the thermal degradation of a polyester/cellulose fabric substrate ("article") treated with a fluorotelomer-based acrylic polymer under laboratory conditions conservatively representing typical combustion conditions of time, temperature, and excess air level in a municipal incinerator, with an average temperature of 1000°C or greater over approximately 2 second residence time.

Result : Polyester/cellulose fabric treated with a fluorotelomer-based acrylic polymer is destroyed and no detectable amount of PFOA is formed under typical municipal incineration conditions. Therefore, textiles and paper treated with such a fluorotelomer-based acrylic polymer disposed of in municipal waste and incinerated are expected to be destroyed and not be a significant source of PFOA in the environment.

Test substance : PFOA

08.12.2005 (637)

Memo : Possibility of recovery/recycling

Method : A process for the recovery of fluorinated emulsifier acids from wastewater, which comprises firstly removing fine solids which are held in a stable colloidal fine distribution by the fluorinated emulsifier acids and/or material

which can be converted into fine solids from the wastewater and subsequently binding the fluorinated emulsifier acids on an anion-exchange resin. The fine solids can be precipitated, mechanically removed, or separated off by sedimentation or by flotation.

04.11.2005 (261)

Memo : Possibility of recovery/recycling

Method : A salt of a divalent metal and a salt of a trivalent metal are added to a solution containing a fluorine compound to precipitate a lamellar composite hydroxide containing the fluorine compound between lamellae to thereby fix a large proportion of the fluorine compound. According to need, the lamellar composite hydroxide precipitate is recovered, and the fluorine compound or a salt thereof each present between the lamellae can be isolated. Consequently, the burden to be imposed by the fluorine compound on the environment or an ecological system can be lessened.

07.11.2005 (266)

Memo : Possibility of recovery/recycling

Method : A salt of a divalent metal and a salt of a trivalent metal are added to a solution containing a fluorine compound and a fluoropolymer to precipitate a lamellar composite hydroxide containing the fluorine compound between lamellae and to simultaneously coagulate and precipitate the fluoropolymer suspended in the solution. Thus, a large proportion of the fluorine compound is fixed and separated from the solution together with the fluoropolymer. They are recovered according to need. By this treatment method, a fluorine compound and a fluoropolymer contained in wastewater or the like can be easily separated there from and the burden to be imposed on the environment or an ecological system can be lessened.

07.11.2005 (265)

Memo : Possibility of recovery/recycling

Method : A fluorine-containing emulsifer is removed from a waste solution by using 3 to 10 ion exchange towers filled with weakly basic anion exchange resin and arranged in series. Adsorption is carried out by introducing the waste solution into the first tower while desorption is carried out in the one remaining tower when the fluorine-containing emulsifer is detected in the effluent from the last tower.

Test substance : PFOA

04.11.2005 (269)

Memo : Possibility of recovery/recycling

Method : A method for adsorbing and recovering a fluorine-containing emulsifier at a high recovery from coagulation waste water of a fluoropolymer, is presented. An inorganic acid is added to coagulation waste water of a fluoropolymer containing a fluorine-containing emulsifier, to adjust the pH of the waste water to a level of at least 1 and less than 6, then a metal chloride having a solubility of at least 5 mass% in water at 25°C, or a hydrate of the metal chloride, is added to the waste water, to coagulate and remove a solid content and/or a substance convertible to a solid content, contained in the waste water, and then the waste water is contacted to a weakly basic anion exchange resin.

07.11.2005 (268)

Memo : Possibility of recovery/recycling

Method : Fluorine-containing emulsifiers can be recovered from aqueous liquors containing fluorine-containing emulsifiers in concentrations of as low as 1 ppm by mass to 1% by mass (for example, wastewaters from the step of

flocculation of fluoropolymers following the emulsion polymerization or aqueous washings obtained by water-washing the waste gas from the step of drying of fluoropolymers and/or the step of heat treatment thereof) by vacuum-concentrating such an aqueous liquor by the use of a concentrator of evaporation-on-heating-tube-surface type equipped with a heat pump under a pressure of 100 kPa or below at a liquor temperature of 100°C or below to thereby obtain a concentrated aqueous liquor having a fluorine-containing emulsifier concentration of 5% by mass or above and recovering the fluorine-containing emulsifier from the concentrated aqueous liquor. According to the invention, fluorine-containing emulsifiers can be recovered with high recovery from liquors containing such emulsifiers in low concentrations, for example, wastewaters from the flocculation of fluoropolymers.

04.11.2005 (267)

Memo : Possibility of destruction: others

Method : Perfluorooctane sulfonate (PFOS) and PFOA are shown to be globally distributed, environmentally persistent, and bioaccumulative. Although the toxicities of these compounds were reported, the cleanup procedure from the environment is not developed because of their inertness. In this report the sonochemical degradations of PFOS and PFOA to the products through the fission of the perfluorocarbon chains were observed and the half-life times of the PFOS and PFOA degradations under an argon atmosphere determined.

Result : The half-life times of PFOS and PFOA degradations under an argon atmosphere were determined to be 43 and 22 minutes, respectively. The shortening of perfluorocarbon chain of PFOS and PFOA leads to the lowering of the toxicity in view of the decrease of the persistence, and the technique would contribute to the remediation of the environmental pollution by these compounds.

08.12.2005 (448)

Memo : Possibility of destruction: others

Result : Perfluorocarboxylic acids are decomposed into fluorocarboxylic acids with lower C number and F- by irradiation of fluorocarboxylic acid-containing aqueous solutions with UV-containing light in the presence of O-containing gases. An aqueous solution of C7F15CO2H was irradiated using a Hg-Xe lamp (250-600 nm) at 25° for 72 hours to form F-, C6F13CO2H, C5F11CO2H, C4F9CO2H, etc.

07.11.2005 (324)

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT