Screening level cumulative risk assessment perfluorinated alkyl acids on human health

Rich Purdy

- Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. Office of Pesticide Programs, US EPA. EPA 2002.

- Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of action. EPA 1999.

Cumulative chemicals should have same “mechanism of toxic action” and “site of toxic effect”.

Or in other words:

Cumulative chemicals have a common mechanism of toxicity.

Common mechanism of toxicity pertains to two or more chemicals that cause a common toxic effect(s) by the same or essentially the same, sequence of major biochemical events (i.e., mode of action)

Proposed Cumulative Class:

Perfluorinated Acids

Currently including:

PFOS and its homologs:
$F(CF2)_xSO3$

PFOA and its homologs:
$F(CF2)_yCO2$

Justification 1

Common mechanism of action

Uncoupling of oxidative phosphorylation is apparently the primary molecular mechanism of toxicity.

References:

- Langley AE, Pilcher GD. 1985. Thyroid, bradycardic and hypothermic effects of perfluoro-n-decanoic acid in rats. Journal of Toxicology and Environmental Health 15:485-491.

- Schnellmann G. 1990. The Cellular Effects of unique pesticide Sulfluramid (N-ethylperfluorooctanesulphonamide) on rabbit renal proximal tubules. Toxic. *In vitro* 4:71-76.

- Wallace KB, Starkov A. 1998. The effect of perfluorinated arylalkylsulfonamides on bioenergetics of rat liver mitochondria. US EPA OPPT AR226-0167

- Starkov AA, Wallace KB. 2002. Structural determinants of fluorochemical-induced mitochondrial dysfunction. Tox Sci 66:244-252.

PFAs shown to be uncouplers

- PFOS
- FOSA (perfluorooctane sulfamide)
- PFHS (perfluorohexane sulfonate
- PFOA
- PFDA (perfluorodecanoic acid)

Justification 1b:

Data supporting uncoupling as a mechanism

Poor body mass gain efficiency is symptom of the uncoupling of oxidative phosphorylation.

Most PFA toxicity studies report loss of weight, poor growth, or poor food conversion efficiency can be calculated from data.

References:

- Covance. 2000.104-week dietary chronic study and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in rats. US EPA OPPT AR226-0956.
- Case MT. 1999. Oral (stomach tube) Developmental toxicity of PFOS in rabbits. US EPA OPPT AR226-0949*.York et al 1999;
- 3M 1987. Two year oral (diet) toxicity / carcinogenicity study of fluorochemical FC-143 in rats. US EPA OPPT AR225-0437
- Campbell SM, Lynn SP, Beavers JB.1993a. Lithium Perfluorooctane Sulfonate [6861D11] A dietary LC50 study with the Northern Bobwhite, Wildlife International Ltd. Project No.: 319-101. Sponsor: SC. Johnson & Son, Inc.
- ---. 1993b. Lithium Perfluorooctane Sulfonate [6861D11] A dietary LC50 study with the Mallard, Wildlife International Ltd. Project No.: 319-102. Sponsor: SC. Johnson & Son, Inc.
- Cook JC, Murray SM, Frame SR, Hurtt ME. 1992. Induction of Leydig Cell Adenomas by Ammonium Perfluorooctanoate: A Possible Endocrine-Related Mechanism. Toxicology and Applied Pharm 113:209-317.
- Borges T, Robertson LW, Peterson RE, Glauert H P. 1992. Dose-related effects of perfluorodecanoic acid on growth, feed intake and hepatic peroxisomal beta-oxidation. Archives of Toxicology 66:18-22.
- George ME, Andersen ME. 1986. Toxic Effects of nonadecafluoro-n-decanoic acid in rats. Toxicology and Applied Pharmacology 85:169-180.

References continued

- Haughom B, Spydevold Ø. 1992. The Mechanism Underlying the Hypolipemic Effect of Perfluorooctanoic acid (PFOA), Perfluorooctane sulphonic acid (PFOSA) and Clofibric Acid. Biochemica et Biophysica Acta 112**:**65-72.

- Goldenthal EI, Jessup DC, Geil RG, Mehring JS. 1978a. Ninety-day subacute Rhesus monkey toxicity study, with Fluorad fluorochemical surfactant FC95. US EPA OPPT AR226-0137

- Goldenthal EI, Jessup DC, Geil RG, Jefferson ND, Arceo RJ. 1978b. Ninety-day subacute rat toxicity study, with Fluorad fluorochemical surfactant FC-95. US EPA OPPT AR226-0141

- Hansen K. 1999a. Laboratory report: analysis of fluorochemicals in wild bird livers. US EPA OPPT AR226-0079

- Langley AE.1990. Effects of perfluoro-n-decanoic acid on the respiratory activity of isolated rat liver mitochondria. J. Toxicol Environ Health 29:329-336.

- Thomford PJ. 1998. 4-Week capsule toxicity studies with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in Cynomolgus monkeys [includes draft final report, cell proliferation report, protocol and memorandum from Marvin Case re histopathology review of liver tissue. US EPA OPPT AR226-0144.

Justification 2

Common sites of toxic effects seen

Similar effects on tissues are observed across the class

- Thymus atrophy
- Thyroid hormone decrease
- Thyroid mass increase
- Liver enlargement

References

- Goldenthal EI, Jessup DC, Geil RG, Mehring JS. 1978a. Ninety-day subacute Rhesus monkey toxicity study, with Fluorad fluorochemical surfactant FC95. US EPA OPPT AR226-0137*.

- Goldenthal EI, Jessup DC, Geil RG, Jefferson ND, Arceo RJ. 1978b. Ninety-day subacute rat toxicity study, with Fluorad fluorochemical surfactant FC-95. US EPA OPPT AR226-0141*

- Covance. 2000.104-week dietary chronic study and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in rats. US EPA OPPT AR226-0956*.

- Van Rafelghem MC, Baskin MJ, Bruner RH, Andersen ME 1987. A time-course study of perfluoro-n-decanoic acid pathology in male Fischer-344 rats. Fund & Appl Toxicol 11:503.

- Van Rafelghem MC, Inhorn SL, Peterson RE. 1987. Effects of perfluorodecanoic acid on thyroid status in rats. Toxicology and Applied Pharmacology 87:430-439.

- Van Rafelghem MC, Mattie DR, Bruner RH, Andersen ME. 1987. Pathological and hepatic ultrastructral effects of a single dose of perfluoro-n-decanoic acid in the rat hamster, mouse, and guinea pig. Fund and Appl Tox 9:522-540.

References, continued

- Langley AE, Pilcher GD. 1985. Thyroid, bradycardic and hypothermic effects of perfluoro-n-decanoic acid in rats. Journal of Toxicology and Environmental Health 15:485-491.29-336.
- Case MT. 1999. Summary PFOS rat two-generation reproduction study. US EPA OPPT AR226-0569
- Metrick M, Marias AJ. 1977. 28-day oral toxicity study with FC-143 in albino rats. US EPA OPPT AR225-0445*
- Thomford PJ. 1998. 4-Week capsule toxicity studies with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in Cynomolgus monkeys [includes draft final report, cell proliferation report, protocol and memorandum from Marvin Case re histopathology review of liver tissue. US EPA OPPT AR226-0144
- Thomford PJ. 2000. 26-week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in Cynomolgus monkeys. US EPA OPPT AR226-0957
- Seacat AM, Hansen K. 2000. Analytical laboratory report from the 26-week capsule toxicity study with Perfluorooctanesulfonic acid potassium salt (T-6295) in Cynomolgus monkeys. US EPA OPPT AR226-0981.
- Thomford PJ 2001. 26-week capsule toxicity study with ammonium perfluorooctanoate in Cynomolgus monkeys. US EPA OPPT AR226-1052a

Structurally Similar

$$F(CF2)_xSO_3$$

$$F(CF2)_yCO_2$$

Reasons for Thymus

- Thymus effects seen in every study in which it was evaluated.
- No NOEL yet established, so could be most sensitive toxic response.
- In early development thymus health is extremely important.

References for Study Used

- Thomford PJ. 2000. 26-week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in Cynomolgus monkeys. US EPA OPPT AR226-0957

- Seacat AM, Hansen K. 2000. Analytical laboratory report from the 26-week capsule toxicity study with Perfluorooctanesulfonic acid potassium salt (T-6295) in Cynomolgus monkeys. US EPA OPPT AR226-0981

Observations of Atrophied Thymus

	Control	Low	Mid	High
Females	0 of 4	4 of 4	4 of 4	3 of 4
Males	1 of 4	2 of 4	3 of 4	2 of 2

- Concentration PFOS in sera of low dose females at end of study: 11.4 – 17 ppm

Identification of fluorochemicals in human sera. III. Pediatric participants in a group A Streptococci clinical trial investigation.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH et al. 2002.

US EPA OPPT AR226-1085.

Chemical	Conc. ppm
Perfluoro sulfonates	
C6	
C7	
PFOS	
C9	
C10	
Perfluoro fatty acids	
C6	
C7	
C8, PFOA	
C9	
C10	
C11	
C12	
C13	
C14	
C15	
C16	
Sum Perfluorinated acids:	

Female rat sera NOELS for PFOS and PFOA

PFOA: 0.15 mg/l

PFOS: 5.3mg/l

Reference:

- Metrick M, Marias AJ. 1977. 28-day oral toxicity study with FC-143 in albino rats. US EPA OPPT AR225-0445
- Belisle J.1978. FC-143 analysis of serum samples from rats from 28 and 90-day studies. US EPA OPPT AR225-0442
- Case 1999. Summary PFOS rat two-generation reproduction study. US EPA OPPT AR226-0569

Chemical	High Conc. ppm	Median Conc. ppm
C6 sulfonate	0.50	0.004
C7 sulfonate	?	?
PFOS	0.22	0.03
C9 sulfonate	?	?
C10 sulfonate	?	?
C6 fatty acid	?	?
C7 fatty acid	?	?
C8, PFOA	0.03	0.004
C9 fatty acid	?	?
C10 fatty acid	?	?
C11 fatty acid	?	?
C12 fatty acid	?	?
C13 fatty acid	?	?
C14 fatty acid	?	?
C15 fatty acid	?	?
C16 fatty acid	?	?

Perfluorodecanesulfonate (PFDS) estimated to be equal to PFOS

Rational: Detected in samples where PFOS levels are close to limits of detection.

Reference:

- Hansen K. 1999. Laboratory report: analysis of fluorochemicals in wild bird livers. US EPA OPPT AR226-0079.
- Hansen K.1999. Analysis of FCs in samples of children's sera. US EPA OPPT AR226-0961

Perfluorodecanoic acid (PFDA) estimated from PFOA level

- Based on bioaccumulation factor (>500 times that of PFOA) and the relative level in a dominate product, Zonyl BA.
-
- References:
- Hansen K. 1999. Report of data for exploratory 28-day oral toxicity study in rats: telomer alcohol, telomer acrylate, PFBS, PFHS, PFOS. US EPA OPPT AR226-0951
- duPont material safety data sheet on Zonyl BA

Concentration (ppm) in rat liver

	Day 1	Day 14	Day 28
PFOA	0.16	0.016	<.003
PFDA	1.69	1.36	2.24
	1.20	1.20	0.81
C12	0.117	0.085	0.101
	0.029	0.035	0.036

*Gavage telomer alcohol mixture for 28 days. Stopped dosing on day1

Half-lives of PFOS and PFOS in Sera

	Rats	Humans
PFOA	4.8 days	4.4 years
PFOS	7.5 days	8.7 years

Reference:

- Gibson SJ, Johnson JD. 1979. Absorption of FC-143-14C in rats after a single oral dose. US EPA OPPT AR226-0455
- Gibson SJ, Johnson JD. 1979. Absorption of FC-95-14C in rats after a single oral dose. US EPA OPPT AR226-0007
- Burris JM, Lundberg JK, Olsen G, Simpson C, Mandel J. 2002. Determination of serum half-lives of several fluorochemicals. US EPA OPPT AR226-1086

C12 and C14 perfluoro fatty acids estimated from PFDA

Reference:

- Mabury, S. 2002. Fascinating fluoro facts of perfluorinatedalkyl carboxylates and sulfonates. SETAC 2002 meeting presentation.

C9, C11, C13 and C15 estimated to be same as homolog with one less carbon.

Reference:

- Mabury, S. 2002. Fascinating fluoro facts of perfluorinatedalkyl carboxylates and sulfonates. SETAC 2002 meeting presentation.

Estimated Concentration of Perfluorinated Acids in Sera of 2-year-old Girls.

Chemical	Highest Measured Conc. ppm	Estimated **Highest Conc. ppm**	Median Measured Conc. ppm	Estimated **Median Conc. ppm**
Perfluoro sulfonates				
C6	0.50	**0.62**	0.004	**0.005**
PFOS	0.22	**0.22**	0.03	**0.03**
C10	ND	**0.18**	ND	**0.02**
Perfluoro fatty acids				
C8, PFOA	0.03	**0.04**	0.004	**0.005**
C9	ND	**0.04**	ND	**0.005**
C10	ND	**12**	ND	**1.4**
C11	ND	**10**	ND	**1.3**
C12	ND	**19**	ND	**2.3**
C13	ND	**15**	ND	**1.8**
C14	ND	**25**	ND	**3.0**
C15	ND	**20**	ND	**2.0**

Chemical	Highest Measured Conc. ppm	Estimated Highest Conc. ppm	Median Measured Conc. ppm	Estimated Median Conc. ppm
Perfluoro sulfonates				
C6	0.50	0.62	0.004	0.005
PFOS	0.22	0.22	0.03	0.03
C10	ND	0.18	ND	0.02
Perfluoro fatty acids				
C8, PFOA	0.03	0.04	0.004	0.005
C9	ND	0.04	ND	0.005
C10	ND	12	ND	1.4
C11	ND	10	ND	1.3
C12	ND	19	ND	2.3
C13	ND	15	ND	1.8
C14	ND	25	ND	3.0
C15	ND	20	ND	2.0
Sums:		**102**		**12**

Level causing thymus atrophy<11.4