**Abbreviations**

8-dG: 8-hydroxydesoxyguanosine; AFC: EFSA Panel on food additives: flavourings: processing aids and materials in contact with food; ALT: alanine aminotransferase; APFO: ammonium perfluorooctanoate; AST: aspartate aminotransferase; BfR: Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment); BMI: body mass index; BW: body weight; CAR: constitutive androstane receptor; COT: Committee on Toxicity of Chemicals in Food: Consumer Products and the Environment; ECF: electrochemical fluorination; EFSA: European Food Safety Authority; FDA: US Food and Drug Administration; FOSA: perfluorooctyl sulfonamide; FOSE: perfluorooctanesulfonamide ethanol; $FT_4$ free thyroxine; FTOH: fluorotelomer alcohol; GD: gestational day; GJIC: gap junction intercellular communication; HDL: high density lipoprotein; LADD: lifetime average daily dose; $LC_{50}$: lethal concentration with 50% lethality; $LD_{50}$: lethal dose with 50% lethality; L-FABP: liver type fatty acid binding protein; LH: luteinizing hormone; LOAEL: lowest observed adverse effect level; L-PFOA: linear PFOA; L-PFOS linear PFOS; MTE: more typical exposure; *N* (or *n*): number (of samples); n.a.: not analyzed; n.d.: not detected; n.r.: not reported; *N*-EtFOSA: *N*-ethylperfluorooctyl sulfonamide; *N*-EtFOSE: *N*-ethylperfluorooctyl sulfonamide ethanol; NHANES: National Health and Nutrition Examination Survey; NOAEL: no observed adverse effect level; OAT: organic anion transporter; OECD: Organisation for Economic Co-operation and Development; PCB: polychlorinated biphenyls; PFBA: perfluorobutanoic acid; PFBS: perfluorobutanesulfonic acid; PFCs: perfluorinated compounds/ polyfluorinated compounds; PFCA: perfluorinated carboxylic acids; PFDA: perfluorodecanoic acid; PFDoA: perfluorododecanoic acid; PFHpA: perfluoroheptanoic acid; PFHxA: perfluorohexanoic acid; PFHxS: perfluorohexanesulfonic acid; PFNA: perfluorononanoic acid; PFO: deprotonated PFOA; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFPA: perfluorinated phosphonic acid; PFPeA: perfluoropentanoic acid; PFTDA: perfluorotetradecanoic acid; PFUnA: perfluoroundecanoic acid; POP: persistent organic pollutants; POSF: perfluorooctane sulfonyl fluoride; PPAR: peroxisome proliferator activated receptor; PTFE: polytetrafluoroethene; PXR: pregnane × receptor; RME: reasonable maximum exposure; ROS: reactive oxygen species; SMR: standard mortality ratio; SOD: superoxide dismutase; $T_3$: tri-odo thyronine; $T_4$: thyroxine; T-AOC: total antioxidant capacity; TDI: tolerable daily intake; TSH: thyroid stimulating hormone; UBA: Umweltbundesamt (German Environmental Protection Agency); US EPA: United States Environmental Protection Agency.

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**Authors' contributions**

TS had the idea to write such a review and drafted the manuscript. DM evaluated the original literature and participated in drafting the manuscript. HB structured this complex review in chapters and subchapters and participated in drafting the manuscript. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Fricke M, Lahl U: **Risikobewertung von Perfluortensiden als Beitrag zur aktuellen Diskussion zum REACH-Dossier der EU-Kommission.** *UWSF-Z Umweltchem Ökotox* 2005, **17**:36-49.
2. Fromme H, Schlumer M, Ungewiss J, Roscher E: **Materialien zur Umweltmedizin-Umweltmedizinische Bedeutung perfluorierter Kohlenwasserstoffe (PFC), Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit (Hrsg.), Band 16 der Schriftenreihe.** 2006, ISBN 3-939652-12-1.
3. Umweltbundesamt (UBA): **Perfluorierte Verbindungen: Falscher Alarm oder berechtigte Sorge?** *Februar 2007, Dessau* 2007.
4. Umweltbundesamt (UBA): **Per- und Polyfluorierte Chemikalien.** *Einträge vermeiden-Umwelt schützen. Juli 2009, Dessau-Roβlau* 2009.
5. Weinfurtner K, Kördel W, Bücking M: **Untersuchungen zum Übergang von PFT aus belasteten Böden in Pflanzen.** *Bodenschutz. Ausgabe 03* 2008.
6. Stahl T, Heyn J, Thiele H, Hüther J, Failing K, Georgii S, Brunn H: **Carryover of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) from soil to plants.** *Arch Environ Contam Toxicol* 2009, **57**:289-298.
7. Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbühler K: **Estimating consumer exposure to PFOS and PFOA.** *Risk Anal* 2008, **28**:251-269.
8. Tittlemier SA, Pepper K, Seymour C, Moisey J, Bronson R, Cao XL, Dabeka RW: **Dietary exposure of Canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging.** *J Agric Food Chem* 2007, **55**:3203-3210.
9. Haug LS, Huber S, Schlabach M, Becher G, Thomsen C: **Investigation on per- and polyfluorinated compounds in paired samples of house dust and indoor air from Norwegian homes.** *Environ Sci Technol* 2011, **45**:7991-7998.
10. Haug LS, Huber S, Becher G, Thomsen C: **Characterisation of human exposure pathways to perfluorinated compounds–comparing exposure estimates with biomarkers of exposure.** *Environ Int* 2011, **37**:687-693.
11. Scheringer M, Trudel D, Horowitz L, Wormuth M, Cousins IT, Hungenbühler K: **Konsumentenexposition gegenüber PFOS und PFOA.** *Mitt Umweltchem Ökotox* 2007, **14**:32-36.
12. Vestergren R, Cousins IT: **Tracking the pathways of human exposure to perfluorocarboxylates.** *Environ Sci Technol* 2009, **43**:5565-5575.
13. Fromme H, Midasch O, Twardella D, Angerer J, Boehmer S, Liebl B: **Occurrence of perfluorinated substances in an adult German population in southern Bavaria.** *Int Arch Occup Environ Health* 2007, **80**:313-319.
14. **UK Food Standards Agency: Fluorinated chemicals: UK dietary intakes.** [http://www.food.gov.uk/multimedia/pdfs/fsis1106.pdf].
15. European Food Safety Authority: **Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. Scientific opinion of the panel on contaminants in the food chain.** *EFSA J* 2008, **653**:1-131.
16. Ostertag SK, Tague BA, Humphries MM, Tittlemier SA, Chan HM: **Estimated dietary exposure to fluorinated compounds from traditional foods among Inuit in Nunavut, Canada.** *Chemosphere* 2009, **75**:1165-1172.
17. Bundesinstitut für Risikobewertung (BfR): **Gesundheiltiche Risiken durch PFOS und PFOA in Lebensmitteln sind nach dem derzeitigen wissenschaftlichen Kenntnisstand unwahrscheinlich.** *Stellungnahme Nr. 004/2009* 2008.
18. Skutlarek D, Exner M, Färber H: **Perfluorierte Tenside (PFT) in der aquatischen Umwelt und im Trinkwasser.** *UWSF Z Umweltchem Ökotox* 2006, **18**:151-154.
19. Hölzer J, Midasch O, Rauchfuss K, Kraft M, Reupert R, Angerer J, Kleeschulte P, Marschall N, Wilhelm M: **Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water.** *Environ Health Perspect* 2008, **5**:651-657.
20. Hölzer J, Goeen T, Rauchfuss K, Kraft M, Angerer J, Kleeschulte P, Wilhelm M: **One-year follow-up of perfluorinated compounds in plasma of German residents from Arnsberg formerly exposed to PFOA-contaminated drinking water.** *Int J Hyg Environ Health* 2009, **212**:499-504.
21. Wilhelm M, Hölzer J, Dobler L, Rauchfuss K, Midasch O, Kraft M, Angerer J, Wiesmüller G: **Preliminary observations on perfluorinated compounds in plasma samples (1977-2004) of young German adults from an area with perfluorooctanoate-contaminated drinking water.** *Int J Hyg Environ Health* 2009, **212**:142-145.
22. Wilhelm M, Bergmann S, Dieter HH: **Occurrence of perfluorinated compounds (PFCs) in drinking water of North Rhine-Westphalia, Germany and new approach to assess drinking water contamination by shorter-chained C4-C7 PFCs.** *Int J Hyg Environ Health* 2010, **13**:224-232.
23. Mak YL, Taniyasu S, Yeung LW, Lu G, Jin L, Yang Y, Lam PK, Kannan K, Yamashita N: **perfluorinated compounds in tap water from China and several other countries.** *Environ Sci Technol* 2009, **43**:4824-4829.
24. Rumsby PC, McLaughlin CL, Hall T: **Perfluorooctane sulphonate and perfluorooctanoic acid in drinking and environmental waters.** *Philos Transact A Math Phys Eng Sci* 2009, **367**:4119-4136.

25. D'Eon JC, Crozier PW, Furdui VI, Reiner EJ, Libelo EL, Mabury SA: Perfluorinated phosphonic acids in Canadian surface waters and wastewater treatment plant effluent: discovery of a new class of perfluorinated acids. *Environ Toxicol Chem* 2009, **28**:2101-2107.
26. Stahl T, Ackmann R, Georgii S, Wohlfarth R, Brunn H: Perfluorierte Tenside. Verwendung, Vorkommen und Aufnahme mit Trinkwasser und Nahrung. *Ernährung* 2007, **1**:27-35.
27. Schuetze A, Heberer T, Effkemann S, Juergensen S: Occurrence and assessment of perfluorinated chemicals in wild fish from Northern Germany. *Chemosphere* 2010, **78**:647-652.
28. Berger U, Glynn A, Holmström KE, Berglund M, Ankarberg EH, Törnkvist A: Fish consumption as a source of human exposure to perfluorinated alkyl substances in Sweden-analysis of edible fish from Lake Vättern and the Baltic Sea. *Chemosphere* 2009, **76**:799-804.
29. Ericson I, Martí-Cid R, Nadal M, Van Bavel B, Lindström G, Domingo JL: Human exposure to perfluorinated chemicals through the diet: intake of perfluorinated compounds in foods from the Catalan (Spain) market. *J Agric Food Chem* 2008, **56**:1787-1794.
30. European Food Safety Authority: Results of the monitoring of perfluoroalkylated substances in food in the period 2000-2009. *EFSA J* 2011, **9**:2016.
31. Martin JW, Mabury SA, O'Brien PJ: Metabolic products and pathways of fluorotelomer alcohols in isolated rat hepatocytes. *Chem Biol Interact* 2005, **155**:165-180.
32. Kudo N, Iwase Y, Okayachi H, Yamakawa Y, Kawashima Y: Induction of hepatic peroxisome proliferation by 8-2 telomer alcohol feeding in mice: Formation of perfluorooctanoic acid in the liver. *Toxicol Sci* 2005, **86**:231-238.
33. Bundesinstitut für Risikobewertung: Perfluorchemikalien in Papieren und Kartons für Lebensmittelverpackungen. *Gesundheitliche Bewertung Nr. 049/ 2005* 2005.
34. Powley CR, Michalczyk MJ, Kaiser MA, Buxton W: Determination of perfluorooctanoic acid (PFOA) extractable from the surface of commercial cookware under simulated cooking conditions by LC/MS/ MS. *Analyst* 2005, **130**:1299-1302.
35. Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA: Perfluorochemicals: potential sources of and migration from food packing. *Food Addit Contam* 2005, **22**:1023-1031.
36. Sinclair E, Kim SK, Akinleye HB, Kannan K: Quantitation of gas-phase perfluoroalkyl surfactants and fluorotelomer alcohols released from nonstick cookware and microwave popcorn bags. *Environ Sci Technol* 2007, **41**:1180-1185.
37. Tittlemier SA, Pepper K, Edwards L: Concentrations of perfluorooctanesulfonamides in Canadian total diet study composite food samples collected between 1992 and 2004. *J Agric Food Chem* 2006, **54**:8385-8389.
38. Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D: Perfluorinated compounds-exposure assessment for the general population in western countries. *Int J Hyg Environ Health* 2009, **212**:239-270.
39. Ericson Jogsten I, Perelló G, Llebaria X, Bigas E, Martí-Cid R, Kärrman A, Domingo JL: Exposure to perfluorinated compounds in Catalonia, Spain, through consumption of various raw and cooked foodstuffs, including packaged food. *Food Chem Toxicol* 2009, **47**:1577-1583.
40. D'Eon JC, Simpson AJ, Kumar R, Baer AJ, Mabury SA: Determining the molecular interactions of perfluorinated carboxylic acids with human sera and isolated human serum albumin using nuclear magnetic resonance spectroscopy. *Environ Toxicol Chem* 2010, **29**:1678-1688.
41. Renner R: PFOA in people. *Environ Sci Technol* 2007, **41**:4497-4500.
42. Begley TH, Hsu W, Noonan G, Diachenko G: Food migration of fluorochemical paper additives from food-contact paper into foods and food simulants. *Addit Contam* 2008, **25**:384-390.
43. Lv G, Wang L, Liu S, Li S: Determination of perfluorinated compounds in packaging materials and textiles using pressurized liquid extraction with gas chromatography-mass spectrometry. *Analytical Sciences* 2009, **25**:425-429.
44. Goosey E, Harrad S: Perfluoroalkyl compounds in dust from Asian, Australian, European, and North American homes and UK cars, classrooms, and offices. *Environ Int* 2011, **37**:86-92.
45. Langer V, Dreyer A, Ebinghaus R: Polyfluorinated compounds in residential and nonresidential indoor air. *Environ Sci Technol* 2011, **44**:8075-8081.
46. Huber S, Haug LS, Schlabach M: Per- and polyfluorinated compounds in house dust and indoor air from northern Norway-a pilot study. *Chemosphere* 2011, **84**:1686-1693.
47. Washburn ST, Bingman TS, Braithwaite SK, Buck RC, Buxton LW, Clewell HJ, Haroun LA, Kester JE, Rickard RW, Shipp AM: Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles. *Environ Sci Technol* 2005, **39**:3904-3910.
48. Moriwaki H, Takata Y, Arakawa R: Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. *J Environ Monit* 2003, **5**:753-757.
49. Kubwabo C, Stewart B, Zhu J, Marro L: Occurrence of perfluorosulfonates and other perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. *J Environ Monit* 2005, **7**:1074-1078.
50. Kato K, Calafat AM, Needham LL: Polyfluoroalkyl chemicals in house dust. *Environ Res* 2009, **109**:518-523.
51. Fromme H, Schlummer M, Möller A, Gruber L, Wolz G, Ungewiss J, Böhmer S, Dekant W, Mayer R, Liebl B, Twardella D: Exposure of an adult population to perfluorinated substances using duplicate diet portions and biomonitoring data. *Environ Sci Technol* 2007, **41**:7928-7933.
52. Zhang T, Wu Q, Sun HW, Zhang XZ, Yun SH, Kannan K: Perfluorinated compounds in whole blood samples from infants, children, and adults in China. *Environ Sci Technol* 2010, **44**:4341-4347.
53. Midasch O, Drexler H, Hart N, Beckmann MW, Angerer J: Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study. *Int Arch Occup Environ Health* 2007, **80**:643-648.
54. Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima S, Uno A, Saijo Y, Sata F, Yoshimura Y, Kishi R, Nakazara H: Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human blood and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environ Health Perspect* 2004, **112**:1204-1207.
55. Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Needham LL, Goldman LR: Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* 2007, **115**:1670-1676.
56. Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, Foster WG: Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. *Environ Res* 2008, **108**:56-62.
57. Fei C, McLaughlin JK, Tarone RE, Olsen J: Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect* 2007, **115**:1677-1682.
58. Hinderliter PM, Mylchreest E, Gannon SA, Butenhoff JL, Kennedy GL: Perfluorooctane: placental and lactational transport pharmacokinetics in rats. *Toxicology* 2005, **211**:139-148.
59. Kärrman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, Lignell S, Lindstrom G: Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. *Environ Health Perspect* 2007, **115**:226-230.
60. So MK, Yamashita N, Taniyasu S, Jiang Q, Giesy JP, Chen K, Lam PKS: Health risks in infants associated with exposure to perfluorinated compounds in human breast milk from Zhoushan, China. *Environ Sci Technol* 2006, **40**:2924-2929.
61. Völkel W, Genzel-Broviczeny O, Demmelmair H, Gebauer C, Koletzko B, Twardella D, Raab U, Fromme H: Perfluoroctane sulfonate (PFOS) and perfluoroctanoic acid (PFOA) in human breast milk: results of a pilot study. *Int J Hyg Envirnon Health* 2007, **211**:440-446.
62. Liu J, Li J, Zhao Y, Wang Y, Zhang L, Wu Y: The occurrence of perfluorinated alkyl compounds in human milk from different regions of China. *Environ Int* 2010, **36**:433-438.
63. Tao L, Ma J, Kunisue T, Libelo EL, Tanabe S, Kannan K: Perfluorinated compounds in human breast milk from several Asian countries, and in infant formula and dairy milk from the United States. *Environ Sci Technol* 2008, **42**:8597-8602.
64. Llorca M, Farré M, Picó Y, Teijón ML, Alvarez JG, Barceló D: Infant exposure of perfluorinated compounds: levels in breast milk and commercial baby food. *Environ Int* 2010, **36**:584-592.
65. Jones PD, Hu W, de Coen W, Newsted JL, Giesy JP: Binding of perfluorinated fatty acids to serum proteins. *Environ Toxicol Chem* 2003, **22**:2639-2649.
66. Taves DR: Electrophoretic mobility of serum fluoride. *Nature* 1968, **119**:582-583.

67. Shen YW, Taves DR: **Fluoride concentrations in the human placenta and maternal and cord blood.** *An J Obstet Gynecol* 1974, **119**:205-207.
68. Olsen GW, Burris JM, Mandel JH, Zobel LR: **Serum perfluorooctane and hepatic and lipid clinical chemistry tests in fluorochemical production employees.** *J Occup Environ Med* 1999, **41**:799-806.
69. Olsen GW, Hansen KJ, Stevenson LA, Burris JM, Mandel JH: **Human donor liver and serum concentrations of perfluorooctanesulfonate and other perfluorochemicals.** *Environ Sci Technol* 2003, **37**:888-891.
70. Ehresman DJ, Chang S, Bjork JA, Hart JA, Lieder PH, Wallace KB, Butenhoff JL: **Increased acyl CoA oxidase activity in rats after five consecutive daily doses of perfluorobutanesulfonate, perfluorohexanesulfonate, and perfluorooctanesulfonate.** *Toxicologist* 2007, **96**:179.
71. Kannan K, Corsolini S, Falandysz J, Fillmann G, Kumar KS, Loganathan BG, Mohd MA, Olivero J, Van Wouwe N, Yang JH, Aldous KM: **Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries.** *Environ Sci Technol* 2004, **38**:4489-4495.
72. Kärrman A, Langlois I, van Bavel B, Lindström G, Oehme M: **Identification and pattern of perfluorooctane sulfonate (PFOS) isomers in human serum and plasma.** *Environ Int* 2007, **33**:782-788.
73. Ericson I, Gomez M, Nadal M, van Bavel B, Lindstrom G, Domingo JL: **Perfluorinated chemicals in blood of residents in Catalonia (Spain) in relation to age and gender: a pilot study.** *Environ Int* 2007, **33**:616-623.
74. Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Tully JS, Needham LL: **Serum concentrations of 11 polyfluoroalkyl compounds in the U.S. population: data from the national health and nutrition examination survey (NHANES) 1999-2000.** *Environ Sci Technol* 2007, **41**:2237-2242.
75. Wilhelm M, Angerer J, Fromme H, Hölzer J: **Contribution to the evaluation of reference values for PFOA and PFOS in plasma of children and adults from Germany.** *Int J Hyg Environ Health* 2009, **212**:56-60.
76. Midasch O, Schettgen T, Angerer J: **Pilot study on the perfluorooctanesulfonate and perfluorooctanoate exposure of the German general population.** *Int J Hyg Environ Health* 2006, **209**:489-496.
77. Fromme H, Albrecht M, Angerer J, Drexler H, Gruber L, Schlummer M, Parlar H, Korner W, Wanner A, Heitmann D, Roscher E, Bolte G: **Integrated Exposure Assessment Survey (INES): exposure to persistent and bioaccumulative chemicals in Bavaria, Germany.** *Int J Hyg Environ Health* 2007, **210**:345-349.
78. Kärrman A, van Bavel B, Jarnberg U, Hardell L, Lindstrom G: **Perfluorinated chemicals in relation to other persistent organic pollutants in human blood.** *Chemosphere* 2006, **64**:1582-1591.
79. Bischel HN, Macmanus-Spencer LA, Luthy RG: **Noncovalent interactions of long-chain perfluoroalkyl acids with serum albumin.** *Environ Sci Technol* 2010, **44**:5263-5269.
80. Chen YM, Guo LH: **Fluorescence study on site-specific binding of perfluoroalkyl acids to human serum albumin.** *Arch Toxicol* 2009, **83**:255-261.
81. Calafat AM, Needham LL, Kuklenyik Z, Reidy JA, Tully JS, Aguilar-Villalobos M, Naeher LP: **Perfluorinated chemicals in selected residents of the American continent.** *Chemosphere* 2006, **63**:490-496.
82. Harada K, Saito N, Inoue K, Yoshinaga T, Watanabe T, Sasaki S, Kamiyama S, Koizumi A: **The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years.** *J Occup Health* 2004, **46**:141-147.
83. Kärrman A, Mueller JF, van Bavel B, Harden F, Toms LM, Lindstrom G: **Levels of 12 perfluorinated chemicals in pooled australian serum, collected 2002-2003, in relation to age, gender, and region.** *Environ Sci Technol* 2006, **40**:3742-3748.
84. Rylander C, Brustad M, Falk H, Sandanger TM: **Dietary predictors and plasma concentrations of perfluorinated compounds in a coastal population from Northern Norway.** *J Environ Public Health* 2010.
85. Olsen GW, Huang H-Y, Helzlsouer KJ, Hansen KJ, Butenhoff JL, Mandel JH: **Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood.** *Environ Health Perspect* 2005, **113**:539-545.
86. Liu C, Deng J, Yu L, Ramesh M, Zhou B: **Endocrine disruption and reproductive impairment in zebrafish by exposure to 8:2 fluorotelomer alcohol.** *Aquat Toxicol* 2010, **96**:70-76.
87. Liu W, Li X, Xu L, Liu L, Jin Y, Sato I, Tsuda S: **Influence of gestation, regular bleeding and intermittent exposure on blood perfluorooctane sulfonate levels in mice: potential factors inducing sex difference and affecting exposure evaluation.** *J Toxicol Sci* 2010, **35**:309-316.
88. Rylander C, Sandanger TM, Frøyland L, Lund E: **Dietary patterns and plasma concentrations of perfluorinated compounds in 315 Norwegian women: the NOWAC postgenome study.** *Environ Sci Technol* 2010, **44**:5225-5232.
89. Hanssen L, Röllin H, Odland JØ, Moe MK, Sandanger TM: **Perfluorinated compounds in maternal serum and cord blood from selected areas of South Africa: results of a pilot study.** *J Environ Monit* 2010, **12**:1355-1361.
90. Hemat H, Wilhelm M, Völkel W, Mosch C, Fromme H, Wittsiepe J: **Low serum levels of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) in children and adults from Afghanistan.** *Sci Total Environ* 2010, **408**:3493-3495.
91. Calafat A, Kuklenyik Z, Reidy JA, Tully JS, Needham LL: **Perfluorochemicals in residents of the United States in 2001 through 2002.** *"Fluoros" 9th International Symposium on Fluorinated Alkyl Organics in the Environment: August 19-20 2005; Toronto* Toronto; University of Toronto; 2005.
92. Holmström KE, Berglund M, Järnberg U: **Exposure to perfluorinated acids in 108 Swedish women in relation to methylmercury and fish consumption.** *Fluoros 9th International Symposium on Fluorinated Alkyl Organics in the Environment August 19-20 2005; Toronto* Toronto; University of Toronto; 2005.
93. Falandysz J, Taniyasu S, Gulkowska A, Yamada N, Schulte-Oehlmann U: **Is fish a major source of fluorinated surfactants and repellents in humans living on the Baltic coast?** *Environ Sci Technol* 2006, **40**:748-751.
94. Jin Y, Saito N, Harada KH, Inoue K, Koizumi A: **Historical trends in human serum levels of perfluorooctanoate and perfluorooctane sulfonate in Shenyang, China.** *Tohoku J Exp Med* 2007, **212**:63-70.
95. Calafat AM, Wong L-Y, Kuklenyik Z, Reidy JA, Needham LL: **Polyfluoroalky Chemicals in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000.** *Environ Health Perspect* 2007, **115**:1596-1602.
96. De Silva AO, Mabury SA: **Isomer distribution of perfluorocarboxylates in humanblood: potential correlation to source.** *Environ Sci Technol* 2006, **40**:2903-2909.
97. Gibson SJ, Johnson JD: **Absorption of FC-143-14C in Rats After a Single Oral Dose.** Riker Laboratories, Inc., Subsidiary of 3M, St. Paul MN, U.S. EPA Public Docket AR-226-0455, Washington, DC; 1979.
98. Johnson JD, Gibson SJ, Ober RF: *Absorption of FC-95-14C in rats after a single oral dose* Project No. 890310200. Riker Laboratories, Inc., Subsidiary of 3 M, St. Paul MN. (U.S. EPA Docket No. 8(e)HQ-1180-00374); 1979.
99. Kennedy GL Jr: **Dermal toxicity of ammonium perfluorooctanoate.** *Toxicol Appl Pharmacol* 1985, **81**:348-355.
100. Kennedy GL Jr, Hall GT, Brittelli MR, Barnes JR, Chen HC: **Inhalation toxicity of ammonium perfluorooctanoate.** *Food Chem Toxicol* 1986, **24**:1325-1329.
101. Kudo N, Kawashima Y: **Toxicity and toxicokinetics of perfluorooctanoic acid in humans and animals.** *J Toxicol Sci* 2003, **28**:49-57.
102. Fasano WJ, Carpenter SC, Gannon SA, Snow TA, Stadler JC, Kennedy GL, Buck RC, Korzeniowski SH, Hinderliter PM, Kemper RA: **Absorption, distribution, metabolism and elimination of 8-2 fluorotelomer alcohol in the rat.** *Toxicol Sci* 2006, **91**:341-355.
103. Han X, Snow TA, Kemper RA, Jepson GW: **Binding of perfluorooctanoic acid to rat and human plasma proteins.** *Chem Res Toxicol* 2003, **16**:775-781.
104. Lübker DJ, Hansen KJ, Bass NM, Butenhoff JL, Seacat AM: **Interactions of fluorochemicals with rat liver fatty acid-binding protein.** *Toxicology* 2002, **176**:175-185.
105. Ylinen M, Auriola S: **Tissue distribution and elimination of perfluorodecanoic acid in the rat after single intraperitoneal administration.** *Pharmacol Toxicol* 1990, **66**:45-48.
106. Qin P, Liu R, Pan X, Fang X, Mou Y: **Impact of carbon chain length on binding of perfluoroalkyl acids to bovine serum albumin determined by spectroscopic methods.** *J Agric Food Chem* 2010, **58**:5561-5567.
107. Austin ME, Kasturi BS, Barber M, Kannan K, Mohan-Kumar PS, MohanKumar SMJ: **Neuroendocrine effects of perfluorooctane sulfonate in rats.** *Environ Health Perspect* 2003, **111**:1485-1489.
108. Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, Butenhoff JL: **Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats.** *Toxicology* 2003, **183**:117-131.
109. Yoo H, Guruge KS, Yamanaka N, Sato C, Mikami O, Miyazaki S, Yamashita N, Giesy JP: **Depuration kinetics and tissue disposition of PFOA and PFOS in**

white leghorn chickens (*Gallus gallus*) administered by subcutaneous implantation. *Ecotoxicol Environ Saf* 2009, **72**:26-36.
110. Han X, Yang C-H, Snajdr SI, Nabb DL, Mingoia RT: Uptake of perflurooctanoate in freshly isolated hepatocytes from male and female rats. *Toxicol Lett* 2008, **181**:81-86.
111. Kudo N, Sakai A, Mitsumoto A, Hibino Y, Tsuda T, Kawashima Y: Tissue distribution and hepatic subcellular distribution of perfluorooctanoic acid at low dose are different from those at high dose in rats. *Biol Pharm Bull* 2007, **30**:1535-1540.
112. Tan YM, Clewell HJ III, Andersen ME: Time dependencies in perfluorooctylacids disposition in rat and monkeys: a kinetic analysis. *Toxicol Lett* 2008, **177**:38-47.
113. Liu L, Jin YH, Wang L, Yu HY, Liu W, Yu QL, Wang K, Liu B, Wang J: Effects of perfluorooctane sulfonate on learning and memory of rat pups. *Zhonghua Yu Fang Yi Xue Za Zhi* 2009, **43**:622-627.
114. Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH, Butenhoff JL, Stevenson LA, Lau C: Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse I. Maternal and prenatal evaluations. *Toxicol Sci* 2003, **74**:369-381.
115. Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J: Perfluoroalkyl acids: a review of monitoring and toxicological findings. *Toxicol Sci* 2007, **99**:366-394.
116. Peng H, Wei Q, Wan Y, Giesy JP, Li L, Hu J: Tissue distribution and maternal transfer of poly- and perfluorinated compounds in Chinese sturgeon (*Acipenser sinensis*): implications for reproductive risk. *Environ Sci Technol* 2010, **44**:1868-1874.
117. Henderson WM, Smith MA: Perfluorooctanoic acid and perfluorononanoic acid in fetal and neonatal mice following in utero exposure to 8-2 fluorotelomer alcohol. *Toxicol Sci* 2007, **95**:452-461.
118. Butt CM, Muir DC, Mabury SA: Elucidating the pathways of poly- and perfluorinated Acid formation in rainbow trout. *Environ Sci Technol* 2010, **44**:4973-4980.
119. Martin JW, Chan K, Mabury SA, O'Brien PJ: Bioactivation of fluorotelomer alcohols in isolated rat hepatocytes. *Chem Biol Interact* 2009, **177**:196-203.
120. Kudo N, Katakura M, Sato Y, Kawashima Y: Sex hormone-regulated renal transport of perfluorooctanoic acid. *Chem Biol Interact* 2002, **139**:301-316.
121. Van den Heuvel JP, Kuslikis BI, van Rafelghem MJ, Peterson RE: Tissue distribution, metabolism and elimination of perfluorooctanoic acid in male and female rats. *J Biochem Toxicol* 1991, **6**:83-92.
122. Weaver YM, Ehresman DJ, Butenhoff JL, Hagenbuch B: Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. *Toxicol Sci* 2010, **113**:305-314.
123. Johnson JD, Gibson SJ, Ober RE: Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C] perfluorooctanoate or potassium [14C]perfluorooctansulfonate. *Fundam Appl Toxicol* 1984, **4**:972-976.
124. Cui L, Liao CY, Zhou QF, Xia TM, Yun ZJ, Jiang GB: Excretion of PFOA and PFOS in male rats during a subchronic exposure. *Arch Environ Contam Toxicol* 2010, **58**:205-213.
125. Butenhoff JL, Kennedy GL, Frame SR, O'Connor JC, York RG: The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 2004, **196**:95-116.
126. Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A: Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. *Environ Res* 2005, **99**:253-261.
127. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT): COT Statement on the Tolerable Daily Intake for Perfluorooctane Sulfonate. *COT Statement 2006/9* 2006.
128. Seacat AM, Thomford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL: Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. *Toxicol Sci* 2002, **68**:249-264.
129. Benskin JP, De Silva AO, Martin LJ, Arsenault G, McCrindle R, Riddell N, Mabury SA, Martin JW: Disposition of perfluorinated acid isomers in Sprague-Dawley rats; part 1: single dose. *Environ Toxicol Chem* 2008, **28**:542-554.
130. De Silva AO, Benskin JP, Martin LJ, Arsenault G, McCrindle R, Riddell N, Martin JW, Mabury SA: Disposition of perfluorinated acid isomers in sprague-dawley rats; part 2: subchronic dose. *Environ Tox Chem* 2008, **28**:555-567.
131. Olsen GW, Butenhoff JL, Zobel LR: Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. *Reprod Toxicol* 2009, **27**:212-230.
132. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR: Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* 2007, **115**:1298-1305.
133. Hundley SG, Sarrif AM, Kennedy GL: Absorption, distribution and excretion of ammonium perfluorooctanoate (APFO) after oral administration to various species. *Drug Chem Toxicol* 2006, **29**:137-145.
134. Organisation for Economic Cooperation and Development: Hazard assessment of perfluorooctane sulfonate (PFOS) and its salts. *November 21, ENV/JM/RD 17/Final* 2002.
135. Glaza S: Acute Dermal Toxicity Study of T-6342 in Rabbits. *Coming Hazelton Inc., Madison WI., 3 M Company, St Paul. US EPA AR226-0427* 1995.
136. Biesemeier JA, Harris DL: Eye and Skin Irritation Report on Sample T-1117. *Report. Project No. 4102871, WARF Institute Inc* 1974.
137. Ji K, Kim Y, Oh S, Ahn B, Jo H, Choi K: Toxicity of perfluorooctane sulfonic acid and perfluorooctanoic acid on freshwater macroinvertebrates (*Daphnia magna* and *Moina macrocopa*) and fish (*Oryzias latipes*). *Environ Toxicol Chem* 2008, **27**:2159-2168.
138. Christopher B, Martin JW: *28-Day Oral Toxicity Study with FC-143 in Albino Mice* 8532-10655, T-1742CoC. Industrial Bio-Test Laboratories, Inc; 1977.
139. Metrick M, Marias AJ: *28-Day oral toxicity study with FC-143 in albino rats* 8532-10654, T-1742CoC. Industrial Bio-Test Laboratories, Inc; 1977.
140. So MK, Miyake Y, Yeung WY, Ho YM, Taniyasu S, Rostkowski P, Yamashita N, Zhou BS, Shi XJ, Wang JX, Giesy JP, Yu H, Lam PK: Perfluorinated compounds in the Pearl River and Yangtze River of China. *Chemosphere* 2007, **68**:2085-2095.
141. Perkins RG, Butenhoff JL, Kennedy GL Jr, Palazzolo MJ: 13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. *Drug Chem Toxicol* 2004, **27**:361-378.
142. Loveless SE, Finlay C, Everds NE, Frame SR, Gillies PJ, O'Connor JC, Powley CR, Kennedy GL: Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology* 2006, **220**:203-217.
143. Curran I, Hierlihy SL, Liston V, Pantazopoulos P, Nunnikhoven A, Tittlemier S, Barker M, Trick K, Bondy G: Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *J Toxicol Environ Health A* 2008, **71**:1526-1541.
144. Cui L, Zhou QF, Liao CY, Fu JJ, Jiang GB: Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. *Arch Environ Contam Toxicol* 2009, **56**:338-349.
145. Goldenthal EI, Jessup DC, Geil RG, Mehring JS: *Ninety-Day Subacute Rhesus Monkey Toxicity Study* 137-092. Internation Research and Development Corporation; 1978.
146. Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G Jr, Lieder P, Olsen G, Thomford P: Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicol Sci* 2002, **69**:244-257.
147. Yang JH: Perfluorooctanoic acid induces peroxisomal fatty acid oxidation and cytokine expression in the liver of male Japanese medaka (*Oryzias latipes*). *Chemosphere* 2010, **81**:548-552.
148. Fang X, Wei Y, Liu Y, Wang J, Dai J: The identification of apolipoprotein genes in rare minnow (*Gobiocypris rarus*) and their expression following perfluorooctanoic acid exposure. *Comp Biochem Physiol C Toxicol Pharmacol* 2010, **151**:152-159.
149. Thomford PJ: *104-week dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS; T-6295) in rats* Covance Laboratories Inc; 2002, 6329-183.
150. Sibinski LJ: *Final report of a two-year oral (diet) toxicity and carcinogenicity study of fluorochemical FC-143 (perfluorooctanane ammonium carboxylate) in rats* 1987, Vol. 1-4, 3 M Company/RIKER, Exp. No. 0281CR0012; 8 EHQ-1087-0394, October 16.
151. Mann PC, Frame SR: *FC-143: Two-year oral toxicity-oncogenicity study in rats: Peer review of ovaries* 2004, DuPont Project ID 15621, June 25, 2004. US. EPA AR226.
152. Hardisty JF, Willson GA, Brown WR, McConnell EE, Frame SR, Gaylor DW, Kennedy GL, Butenhoff JL: Pathology Working Group review and

evaluation of proliferative lesions of mammary gland tissues in female rats fed ammonium perfluorooctanoate (APFO) in the diet for 2 years. *Drug Chem Toxicol* 2010, **33**:131-137.
153. Biegel LB, Hurtt ME, Frame SR, O'Conner JC, Cook JC: Mechanisms of extrahepatic tumour induction by peroxisome proliferators in male CD rats. *Toxicol Sci* 2001, **60**:44-55.
154. Frame SR, McConnell EE: Review of the proliferative lesions of the exocrine pancreas in two chronic studies in rats with ammonium perfluorooctanoate. *DuPont-13788* 2003.
155. Abdellatif AG, Preat V, Taper HS, Roberfroid M: The modulation of rat liver carcinogenesis by perfluorooctanoic acid, a peroxisome proliferator. *Toxicol Appl Pharmacol* 1991, **111**:530-537.
156. Nilsson R, Beije B, Preat V, Erixon K, Ramel C: On the mechanism of the hepatocarcinogenicity of peroxisome proliferators. *Chem-Biol Interact* 1991, **78**:235-250.
157. Murli H: In *Mutagenicity test on T-6564 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests.* Edited by: Vienna VA. Corning Hazleton Inc; 1996:, Study Number: 17750-0-437CO, September 16, 1996. US EPA. AR226-0433.
158. Yao X, Zhong L: Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanic acid. *Mutat Res* 2005, **587**:38-44.
159. Takagi A, Umemura T, Hasegawa R, Kurokawa Y: Short-term exposure to the peroxisome proliferators perfluorooctanoic acid and perfluorodecanoic acid causes significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats. *Cancer Lett* 1991, **57**:55-60.
160. Lau C, Butenhoff JL, Rogers JM: The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicol Appl Pharmacol* 2004, **198**:231-241.
161. Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, Strynar MJ: Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicol Sci* 2006, **90**:510-518.
162. Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL, Stevenson LA: Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci* 2003, **74**:382-392.
163. Lübker DJ, Case MT, York RG, Moore JA, Hansen KJ, Butenhoff JL: Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology* 2005, **215**:126-148.
164. Christian MS, Hoberman AM, York RG: In *Combined oral (gavage) fertility, developmental and perinatal/postnatal reproduction toxicity study of N-EtFOSE in rats.* Edited by: Horsham PA. Argus Research Laboratories, Inc; 1999:, US EPA Administrative Record, AR-226-0552.
165. Butenhoff JL, Kennedy GL, Hinderliter PM, Lieder PH, Jung R, Hansen KJ, Gorman GS, Noker PE, Thomford PJ: Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. *Toxicol Sci* 2004, **82**:394-406.
166. York RG, Kennedy GL Jr, Olsen GW, Butenhoff JL: Male reproductive system parameters in a two-generation reproduction study of ammonium perfluorooctanoate in rats and human relevance. *Toxicology* 2010, **271**:64-72.
167. Grasty RC, Wolf DC, Grey BE, Lau CS, Rogers JM: Prenatal window of susceptibility to perfluorooctane sulfonate-induced neonatal mortality in the Sprague-Dawley rat. *Birth Defects Res B Dev Reprod Toxicol* 2003, **68**:465-471.
168. Grasty RC, Bjork JA, Wallace KB, Lau CS, Rogers JM: Effects of prenatal perfluorooctane sulfo-nate (PFOS) exposure on lung maturation in the perinatal rat. *Birth Defects Res B Dev Reprod Toxicol* 2005, **74**:405-416.
169. Wolf CJ, Fenton SE, Schmid JE, Calafat AM, Kuklenyik Z, Bryant XA, Thibodeaux J, Das KP, White SS, Lau CS, Abbott BD: Developmental toxicity of per-fluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. *Toxicol Sci* 2007, **95**:462-473.
170. Lübker DJ, York RG, Hansen KJ, Moore JA, Butenhoff JL: Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. *Toxicology* 2005, **215**:149-169.
171. Yu WG, Liu W, Jin YH, Liu XH, Wang FQ, Liu L, Nakayama SF: Prenatal and postnatal impact of perfluorooctane sulfonate (PFOS) on rat development: a cross-foster study on chemical burden and thyroid hormone system. *Environ Sci Technol* 2009, **43**:8416-8422.
172. Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, Nakayama S, Lindstrom AB, Strynar MJ, Lau C: Perfluorooctanoic acid induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator activated receptor-alpha. *Toxicol Sci* 2007, **98**:571-581.
173. Abbott BD: Review of the expression of peroxisome proliferator-activated receptors alpha (PPAR alpha), beta (PPAR beta) and gamma (PPAR gamma) in rodent and human development. *Reprod Toxicol* 2009, **27**:246-257.
174. Yanai J, Dotan S, Goz R, Pinkas A, Seidler FJ, Slotkin TA, Zimmerman F: Exposure of developing chicks to perfluorooctanoic acid induces defects in prehatch and early posthatch development. *J Toxicol Environ Health A* 2008, **71**:131-133.
175. Peden-Adams MM, Stuckey JE, Gaworecki KM, Berger-Ritchie J, Bryant K, Jodice PG, Scott TR, Ferrario JB, Guan B, Vigo C, Boone JS, McGuinn WD, DeWitt JC, Keil DE: Developmental toxicity in white leghorn chickens following in ovo exposure to perfluorooctane sulfonate (PFOS). *Reprod Toxicol* 2009, **27**:307-318.
176. Molina ED, Balander R, Fitzgerald SD, Giesy JP, Kannan K, Mitchell R, Bursian SJ: Effects of air cell injection of perfluorooctane sulfonate before incubation on development of the white Leghorn chicken (*Gallus domesticus*) embryo. *Environ Toxicol Chem* 2006, **25**:227-232.
177. Newsted JL, Coady KK, Beach SA, Butenhoff JL, Gallagher S, Giesy JP: Effects of perfluorooctane sulfonate on mallard and northern bobwhite quail exposed chronically via the diet. *Environ Toxicol Pharmacol* 2007, **23**:1-9.
178. Ankley GT, Kuehl DW, Kahl MD, Jensen KM, Butterworth BC, Nichols JW: Partial life-cycle toxicity and bioconcentration modeling of perfluorooctanesulfonate in the Northern leopard frog (*Rana pipiens*). *Environ Toxicol Chem* 2004, **23**:2745-2755.
179. Ankley GT, Kuehl DW, Kahl MD, Jensen KM, Linnum A, Leino RL, Villeneuve DA: Reproductive and developmental toxicity and bioconcentration of perfluorooctanesulfonate in a partial lifecycle test with the fathead minnow (*Pimephales promelas*). *Environ Toxicol Chem* 2005, **24**:2316-2324.
180. Das KP, Grey BE, Zehr RD, Wood CR, Butenhoff JL, Chang SC, Ehresman DJ, Tan YM, Lau C: Effects of perfluorobutyrate exposure during pregnancy in the mouse. *Toxicol Sci* 2008, **105**:173-181.
181. York RG: *Oral (gavage) combined repeated dose toxicity study of T-7706 with the reproduction/developmental toxicity screening test* 2003, 3 M Sponsor Study Number T-7706.1. US EPA Administrative Record, AR-226-1523.
182. Harris MW, Birnbaum LS: Developmental toxicity of perfluorodecanoic acid in C57BL/6N mice. *Fundam Appl Toxicol* 1989, **12**:442-448.
183. Feng Y, Shi Z, Fang X, Xu M, Dai J: Perfluorononanoic acid induces apoptosis involving the Fas death receptor signaling pathway in rat testis. *Toxicol Lett* 2009, **190**:224-230.
184. Harada KH, Ishii TM, Takatsuka K, Koizumi A, Ohmori H: Effects of perfluorooctane sulfonate on action potentials and currents in cultured rat cerebellar Purkinje cells. *Biochem Biophys Res Commun* 2006, **351**:240-245.
185. Kovarova J, Svobodova Z: Perfluorinated compounds: occurrence and risk profile. *Neuro Endocrinol Lett* 2008, **29**:599-608.
186. Slotkin TA, MacKillop EA, Melnick RL, Thayer KA, Seidler FJ: Developmental neurotoxicity of perfluorinated chemicals modeled in vitro. *Environ Health Perspect* 2008, **116**:716-722.
187. Liao C, Wang T, Cui L, Zhou Q, Duan S, Jiang G: Changes in synaptic transmission, calcium current, and neurite growth by perfluorinated compounds are dependent on the chain length and functional group. *Environ Sci Technol* 2009, **43**:2099-2104.
188. Johansson N, Fredriksson A, Eriksson P: Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice. *Neurotoxicology* 2008, **29**:160-169.
189. Johansson N, Eriksson P, Viberg H: Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain. *Toxicol Sci* 2009, **108**:412-418.
190. Löffler G, Petrides P, Heinrich P: *Biochemie & Pathobiochemie. 8. Auflage* Heidelberg: Springer Medizin Verlag; 2007.
191. Sato I, Kawamoto K, Nishikawa Y, Tsuda S, Yoshida M, Yaegashi K, Saito N, Liu W, Jin Y: Neurotoxicity of perfluorooctane sulfonate (PFOS) in rats and mice after single oral exposure. *J Toxicol Sci* 2009, **34**:569-574.
192. Liu L, Liu W, Song J, Yu H, Jin Y, Oami K, Sato I, Saito N, Tsuda S: A comparative study on oxidative damage and distributions of

perfluorooctane sulfonate (PFOS) in mice at different postnatal developmental stages. *Toxicol Sci* 2009, **34**:245-254.
193. Liu X, Liu W, Jin Y, Yu W, Wang F, Liu L: Effect of gestational and lactational exposure to perfluorooctanesulfonate on calcium-dependent signaling molecules gene expression in rats' hippocampus. *Arch Toxicol* 2010, **84**:71-79.
194. Pinkas A, Slotkin TA, Brick-Turin Y, Van der Zee EA, Yanai J: Neurobehavioral teratogenicity of perfluorinated alkyls in an avian model. *Neurotoxicol Teratol* 2010, **32**:182-186.
195. Langley AE, Pilcher GD: Thyroid, bradycardic and hypothermic effects of perfluoro-n-decanoic acid in rats. *J Toxicol Environ Health* 1985, **15**:485-491.
196. Gutshall DM, Pilcher GD, Langley AE: Effect of thyroxine supplementation on the response to perfluoro-n-decanoic acid (PFDA) in rats. *J Toxicol Environ Health* 1988, **24**:491-498.
197. Weiss JM, Andersson PL, Lamoree MH, Leonards PE, van Leeuwen SP, Hamers T: Competitive binding of poly- and perfluorinated compounds to the thyroid hormone transport protein transthyretin. *Toxicol Sci* 2009, **109**:206-216.
198. Chang SC, Thibodeaux JR, Eastvold ML, Ehresman DJ, Bjork JA, Froehlich JW, Lau C, Singh RJ, Wallace KB, Butenhoff JL: Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). *Toxicology* 2008, **243**:330-339.
199. Benninghoff AD, Field JA, Williams DE: Assessment of the estrogen activity of perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS) and other structurally diverse perfluorinated chemicals in rainbow trout. *Toxicologist CD* 2007, **96**:110.
200. Wei Y, Dai J, Liu M, Wang J, Xu M, Zha J, Wang Z: Estrogen-like properties of perfluorooctanoic acid as revealed by expressing hepatic estrogen-responsive genes in rare minnows (*Gobiocypris rarus*). *Environ Toxicol Chem* **26**:2440-2447.
201. Zhao B, Chu Y, Hardy DO, Li XK, Ge RS: Inhibition of 3beta- and 17beta-hydroxysteroid dehydrogenase activities in rat Leydig cells by perfluorooctane acid. *J Steroid Biochem Mol Biol* 2010, **118**:13-17.
202. Zhao Y, Tan YS, Haslam SZ, Yang C: Perfluorooctanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57BL/6 mice. *Toxicol Sci* 2010, **115**:214-224.
203. Maras M, Vanparys C, Muylle F, Robbens J, Berger U, Barber JL, Blust R, De Coen W: Estrogen-like properties of fluorotelomer alcohols as revealed by MCF-7 breast cancer cell proliferation. *Environ Health Perspect* 2006, **114**:100-105.
204. Shi Z, Zhang H, Liu Y, Xu M, Dai J: Alterations in gene expression and testosterone synthesis in the testes of male rats exposed to perfluorododecanoic acid. *Toxicol Sci* 2007, **98**:206-215.
205. Shi Z, Ding L, Zhang H, Feng Y, Xu M, Dai J: Chronic exposure to perfluorododecanoic acid disrupts testicular steroidogenesis and the expression of related genes in male rats. *Toxicol Lett* 2009, **188**:192-200.
206. Yang Q, Xie Y, Depierre JW: Effects of peroxisome proliferators on the thymus and spleen of mice. *Clin Exp Immunol* 2000, **122**:219-226.
207. Yang Q, Abedi-Valugerdi M, Xie Y, Zhao X, Moller G, Nelson BD, DePierre JW: Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid. *Int Immunopharmacol* 2002, **2**:289-397.
208. Yang Q, Xie Y, Alexson SEH, Nelson BD, DePierre JW: Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodilation caused by peroxisome proliferators in mice. *Biochem Pharmacol* 2002, **63**:1893-1900.
209. Fang X, Zhang L, Feng Y, Zhao Y, Dai J: Immunotoxic effects of perfluorononanoic acid on BALB/c mice. *Toxicol Sci* 2008, **105**:312-321.
210. Peden-Adams MM, Keller JM, Eudaly JG, Berger J, Gilkeson GS, Keil DE: Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicol Sci* 2008, **104**:144-154.
211. Keil DE, Mehlmann T, Butterworth L, Peden-Adams MM: Gestational exposure to perfluorooctane sulfonate suppresses immune function in B6C3F1 mice. *Toxicol Sci* 2008, **103**:77-85.
212. Qazi MR, Bogdanska J, Butenhoff JL, Nelson BD, DePierre JW, Abedi-Valugerdi M: High-dose, short-term exposure of mice to perfluorooctanesulfonate (PFOS) or perfluorooctanoate (PFOA) affects the number of circulating neutrophils differently, but enhances the inflammatory responses of macrophages to lipopolysaccharide (LPS) in a similar fashion. *Toxicology* 2009, **262**:207-214.
213. Qazi MR, Nelson BD, Depierre JW, Abedi-Valugerdi M: 28-Day dietary exposure of mice to a low total dose (7 mg/kg) of perfluorooctanesulfonate (PFOS) alters neither the cellular compositions of the thymus and spleen nor humoral immune responses: Does the route of administration play a pivotal role in PFOS-induced immunotoxicity? [abstract]. *Toxicology* 2009, **267**:132-139.
214. Guruge KS, Hikono H, Shimada N, Murakami K, Hasegawa J, Yeung LW, Yamanaka N, Yamashita N: Effect of perfluorooctane sulfonate (PFOS) on influenza A virus-induced mortality in female B6C3F1 mice. *J Toxicol Sci* 2009, **3**:687-691.
215. DeWitt JC, Copeland CB, Luebke RW: Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicol Sci* 2009, **109**:106-112.
216. DeWitt JC, Shnyra A, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, Luster MI: Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha. *Crit Rev Toxicol* 2009, **39**:76-94.
217. Hu XZ, Hu DC: Effects of perfluorooctanoate and perfluorooctane sulfonate exposure on hepatoma Hep G2 cells. *Arch Toxicol* 2009, **83**:851-861.
218. Eriksen KT, Raaschou-Nielsen O, Sørensen M, Roursgaard M, Loft S, Møller P: Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. *Mutat Res* 2010, **700**:39-43.
219. Qian Y, Ducatman A, Ward R, Leonard S, Bukowski V, Lan Guo N, Shi X, Vallyathan V, Castranova V: Perfluorooctane sulfonate (PFOS) induces reactive oxygen species (ROS) production in human microvascular endothelial cells: role in endothelial permeability. *J Toxicol Environ Health A* 2010, **73**:819-836.
220. Sohlenius AK, Eriksson AM, Hogstrom C, Kimland M, DePierre JW: Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid β-oxidation and other activities known to be affected by peroxisome proliferators in mouse liver. *Pharmacol Toxicol* 1993, **72**:90-93.
221. Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ: Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-alpha, -beta, and -gamma, liver × receptor-beta, and retinoid × receptor-alpha. *Toxicol Sci* 2006, **92**:476-489.
222. Ikeda T, Aiba K, Fukuda K, Tanaka M: The induction of peroxisome proliferation in rat liver by perfluorinated fatty acids, metabolically inert derivatives of fatty acids. *J Biochem* 1985, **98**:475-482.
223. Sohlenius AK, Andersson K, DePierre JW: The effects of perfluorooctanoic acid on hepatic peroxisome proliferation and related parameters show no sex-related differences in mice. *Biochem J* 1992, **285**:779-783.
224. Pastoor TP, Lee KP, Perri M, Gillies PJ: Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. *Exp Mol Pathol* 1987, **47**:98-109.
225. Shipley JM, Hurst CH, Tanaka SS, DeRoos FL, Butenhoff JL, Seacat AM, Waxman DJ: Trans-activation of PPARa and induction of PPARa target genes by perfluorooctane-based chemicals. *Toxicol Sci* 2004, **80**:151-160.
226. Maloney EK, Waxman DJ: Trans-activation of PPARa and PPARc by structurally diverse environmental chemicals. *Toxicol Appl Pharmacol* 1999, **161**:209-218.
227. Takacs ML, Abbott BD: Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. *Toxicol Sci* 2007, **95**:108-117.
228. Nakamura T, Ito Y, Yanagiba Y, Ramdhan DH, Kono Y, Naito H, Hayashi Y, Li Y, Aoyama T, Gonzalez FJ, Nakajima T: Microgram-order ammonium perfluorooctanoate may activate mouse peroxisome proliferator-activated receptor alpha, but not human PPARalpha. *Toxicology* 2009, **265**:27-33.
229. Haughom B, Spydevold Ø: The mechanism underlying the hypolipemic effect of perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid. *Biochim Biophys Acta* 1992, **1128**:65-72.
230. Martin MT, Brennan RJ, Hu W, Ayanoglu E, Lau C, Ren H, Wood CR, Corton JC, Kavlock RJ, Dix DJ: Toxicogenomic study of triazole fungicides and perfluoroalkyl acids in rat livers predicts toxicity and categorizes chemicals based on mechanisms of toxicity. *Toxicol Sci* 2007, **97**:595-613.
231. Yin Yeung W, Guruge KS, Yamanaka N, Miyazaki S, Lam PKS, Yamashita N, Geisy JP: Gene expression profiles in rat liver treated with

pentadecafluorooctanic acid (PFOA). *9th "Fluoros" International Symposium on Fluorinated Alkyl Organics in the Environment August 19-20 2005; Toronto* Toronto; University of Toronto; 2005.

232. Guruge KS, Yeung LWY, Yamanaka N, Miyazaki S, Lam PKS, Giesy JP, Jones PD, Yamashita N: Gene expression profiles in rat liver treated with perfluorooctaonic acid (PFOA). *Toxicol Sci* 2006, **89**:93-107.
233. Rosen MB, Thibodeaux JR, Wood CR, Zehr RD, Schmid JE, Lau C: Gene expression profiling in the lung and liver of PFOAexposed mouse fetuses. *Toxicology* 2007.
234. Peters JM, Hennuyer N, Staels B, Fruchart JC, Fievet C, Gonzalez FJ: Alterations in lipoprotein metabolism in peroxisome proliferators-activated receptor alpha-deficient mice. *J Biol Chem* 1997, **272**:27307-27312.
235. Minata M, Harada KH, Kärrman A, Hitomi T, Hirosawa M, Murata M, Gonzalez FJ, Koizumi A: Role of peroxisome proliferator-activated receptor-alpha in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. *Ind Health* 2010, **48**:96-107.
236. Elcombe CR, Elcombe BM, Farrar DG, Foster JR: Characterization of ammonium perfluorooctanic acid (APFO) induced hepatomegaly in rats. *Toxicology* 2007, **240**:172-173.
237. Ren H, Vallanat B, Nelson DM, Yeung LW, Guruge KS, Lam PK, Lehman-McKeeman LD, Corton JC: Evidence for the involvement of xenobiotic-responsive nuclear receptors in transcriptional effects upon perfluoroalkyl acid exposure in diverse species. *Reprod Toxicol* 2009, **27**:266-277.
238. Hu W, Jones PD, Upham BL, Trosko JE, Lau C, Giesy JP: Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague-Dawley rats in vivo. *Toxicol Sci* 2002, **68**:429-436.
239. Upham BL, Park JS, Babica P, Sovadinova I, Rummel AM, Trosko JE, Hirose A, Hasegawa R, Kanno J, Sai K: Structure-activity-dependent regulation of cell communication by perfluorinated fatty acids using in vivo and in vitro model systems. *Environ Health Perspect* 2009, **117**:545-551.
240. Ehresman DJ, Froehlich JW, Olsen GW, Chang SC, Butenhoff JL: Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. *Environ Res* 2007, **103**:176-184.
241. Kudo N, Suzuki-Nakajima E, Mitsumoto A, Kawashima Y: Responses of the liver to perfluorinated fatty acids with different carbon chain length in male and female mice: in relation to induction of hepatomegaly, peroxisomal b-oxidation and microsomal 1-acylglycerophosphocholine acyltransferase. *Biol Pharm Bull* 2006, **29**:1952-1957.
242. Permadi H, Lundgren B, Andesson K, Sundberg C, DePierre JW: Effects of perfluoro fatty acids on peroxisome proliferation on mitochondrial size in mouse liver: dose and time factors and effect of chain length. *Xenobiotic* 1993, **23**:761-770.
243. Wei Y, Shi X, Zhang H, Wang J, Zhou B, Dai J: Combined effects of polyfluorinated and perfluorinated compounds on primary cultured hepatocytes from rare minnow (*Gobiocypris rarus*) using toxicogenomic analysis. *Aquat Toxicol* 2009, **95**:27-36.
244. Jernbro S, Rocha PS, Keiter S, Skutlarek D, Färber H, Jones PD, Giesy JP, Hollert H, Engwall M: Perfluorooctane sulfonate increases the genotoxicity of cyclophosphamide in the micronucleus assay with V79 cells-further proof of alterations in cell membrane properties caused by PFOS. *Env Sci Pollut Res* 2007, **14**:85-87.
245. Watanabe MX, Jones SP, Iwata H, Kim EY, Kennedy SW: Effects of co-exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin and perfluorooctane sulfonate or perfluorooctanoic acid on expression of cytochrome P450 isoforms in chicken (*Gallus gallus*) embryo hepatocyte cultures. *Comp Biochem Physiol C Toxicol Pharmacol* 2009, **149**:605-612.
246. Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS: Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Environ Med* 2003, **60**:722-729.
247. Alexander BH, Olsen GW: Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. *Ann Epidemiol* 2007, **17**:471-478.
248. Grice MM, Alexander BH, Hoffbeck R, Kampa DM: Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *J Occup Environ Med* 2007, **49**:722-729.
249. Gilliland FD, Mandel JS: Mortality among employes of a perfluorooctanoic acid production plant. *J Occup Med* 1993, **35**:950-954.
250. Alexander BH: *Mortality Study of Workers Employed at the 3 M Cottage Grove Facility. Final Report* Division of Environmental and Occupational Health, School of Public Health, University of Minnesota, 2001 EPA AR226-1030a018; 2001.
251. Lundin JI, Alexander BH, Olsen GW, Church TR: Ammonium perfluorooctanoate production and occupational mortality. *Epidemiology* 2009, **20**:921-928.
252. DuPont 2003: Epidemiology surveillance report: cancer incidence for Washington Works site 1959-2001. *US EPA Administrative Record* , AR-226-1307-7.
253. DuPont 2006: Ammonium perfluorooctanoate: phase II. Retrospective cohort analysis related to a serum biomarker of exposure in polymer production plant. *US EPA Administrative Record* , 8EHQ-0381-0394.
254. Gilliland FD, Mandel JS: Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins and cholesterol: a study of occupationally exposed men. *Am J Ind Med* 1996, **29**:560-568.
255. Olsen GW, Burris JM, Burlew MM, Mandel JH: Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug Chem Toxicol* 2000, **23**:603-620.
256. Olsen GW, Zobel LR: Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. *Int Arch Occup Environ Health* 2007, **81**:231-246.
257. Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH: An epidemiological investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. *J Occ Env Med* 1998, **40**:614-622.
258. Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR: Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *J Occup Environ Med* 2007, **49**:872-879.
259. Sakr CJ, Symons JM, Kreckmann KH, Leonard RC: Ischaemic heart disease mortality study among workers with occupational exposure to ammonium perfluorooctanoate. *Occup Environ Med* 2009, **66**:699-703.
260. Costa G, Sartori S, Consonni D: Thirty years of medical surveillance in perfluooctanoic acid production workers. *J Occup Environ Med* 2009, **51**:364-372.
261. Bloom MS, Kannan K, Spliethoff HM, Tao L, Aldous KM, Vena JE: Exploratory assessment of perfluorinated compounds and human thyroid function. *Physiol Behav* 2010, **99**:240-245.
262. Pirali B, Negri S, Chytiris S, Perissi A, Villani L, La Manna L, Cottica D, Ferrari M, Imbriani M, Rotondi M, Chiovato L: Perfluorooctane sulfonate and perfluorooctanoic acid in surgical thyroid specimens of patients with thyroid diseases. *Thyroid* 2009, **19**:1407-1412.
263. Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS: Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect* 2010, **118**:686-692.
264. Emmett EA, Zhang H, Shofer FS, Freeman D, Rodway NV, Desai C, Shaw LM: Community exposure to perfluorooctanoate: relationships beween serum levels and certain health parameters. *J Occup Environ Med* 2006, **48**:771-779.
265. Nelson JW, Hatch EE, Webster TF: Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ Health Perspect* 2010, **118**:197-202.
266. Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V: Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *Am J Epidemiol* 2009, **170**:1268-1278.
267. Steenland K, Fletcher T, Savitz DA: Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). *Environ Health Perspect* 2010, **118**:1100-1108.
268. Anderson-Mahoney P, Kotlerman J, Takhar H, Gray D, Dahlgren J: Self-reported health effects among community residents exposed to perfluorooctanoate. *New Solut* 2008, **18**:129-143.
269. Lin CY, Chen PC, Lin YC, Lin LY: Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. *Diabetes Care* 2009, **32**:702-707.
270. MacNeil J, Steenland NK, Shankar A, Ducatman A: A cross-sectional analysis of type II diabetes in a community with exposure to perfluorooctanoic acid (PFOA). *Environ Res* 2009, **109**:997-1003.

271. Leonard RC, Kreckmann KH, Sakr CJ, Symons JM: **Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers.** *Ann Epidemiol* 2008, **18**:15-22.
272. Washino N, Saijo Y, Sasaki S, Kato S, Ban S, Konishi K, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R: **Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth.** *Environ Health Perspect* 2009, **117**:660-667.
273. Hamm MP, Cherry NM, Martin JW, Bamforth F, Burstyn I: **The impact of isolated maternal hypothyroxinemia on perinatal morbidity.** *J Obstet Gynecol Can* 2009, **31**:1015-1021.
274. Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA: **The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water.** *Reprod Toxicol* 2009, **27**:231-238.
275. Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA: **Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water [abstract].** *Reprod Toxicol* 2010, **29**:147-155.
276. Stein CR, Savitz DA, Dougan M: **Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome.** *Am J Epidemiol* 2009, **170**:837-846.
277. Fei C, McLaughlin JK, Lipworth L, Olsen J: **Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy.** *Environ Health Perspect* 2008, **116**:1391-1395.
278. Fei C, McLaughlin JK, Lipworth L, Olsen J: **Maternal levels of perfluorinated chemicals and subfecundity.** *Hum Reprod* 2009, **24**:1200-1205.
279. Fei C, McLaughlin JK, Lipworth L, Olsen J: **Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding.** *Scand J Work Environ Health* 2010, **36**:413-421.
280. Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM: **Exposure to polyfluoroalkyl chemicals and attention deficit hyperactivity disorder in U.S. children aged 12-15 years.** *Environ Health Perspect* 2010, **118**:1762-1767.
281. Olsen GW, Chang SC, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, Butenhoff JL: **A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys and humans.** *Toxicology* 2009, **256**:65-74.
282. Steenland K, Tinker S, Shankar A, Ducatman A: **Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA.** *Environ Health Perspect* 2010, **118**:229-233.
283. Butenhoff JL, Kennedy GL, Hinderliter PM, Lieder PH, Jung R, Hansen KJ, Gorman GS, Noker PE, Thomford PJ: **Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys.** *Toxicol Sci* 2004, **82**:394-406.
284. Yeung LW, Loi EI, Wong VY, Guruge KS, Yamanaka N, Tanimura N, Hasegawa J, Yamashita N, Miyazaki S, Lam PK: **Biochemical responses and accumulation properties of long-chain perfluorinated compounds (PFOS/PFDA/PFOA) in juvenile chickens (*Gallus gallus*).** *Arch Environ Contam Toxicol* 2009, **57**:377-386.
285. Chang SC, Thibodeaux JR, Eastvold ML, Ehresman DJ, Bjork JA, Froehlich JW, Lau C, Singh RJ, Wallace KB, Butenhoff JL: **Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS).** *Toxicology* 2008, **243**:330-339.
286. Hanhijärvi H, Ophaug RH, Singer L: **The sex-related difference in perfluorooctanoate excretion in the rat.** *Proc Soc Exp Biol Med* 1982, **171**:50-5.
287. Dean WP, Jessup AC: **Acute oral toxicity (LD50) study in rats.** *International research and development corporation, Study 137-091* 1978, US EPA AR226-0419.
288. Li MH: **Toxicity of perfluorooctane sulfonate and perfluorooctanoic acid to plants and aquatic invertebrates.** *Environ Toxicol* 2009, **24**:95-100.
289. Van Gossum H, Bots J, Snijkers T, Meyer J, Van Wassenbergh S, De Coen W, De Bruyn L: **Behaviour of damselfly larvae (*Enallagma cyathigerum*) (Insecta, Odonata) after long-term exposure to PFOS.** *Environ Pollut* 2009, **157**:1332-1336.
290. Goldenthal EI, Jessup DC, Geil RG, Mehring JS: *Ninety-Day Subacute Rat Toxicity Study 137-085* International Research and Development Corporation; 1978.
291. Gortner EG: **Oral Teratology Study of FC-95 in Rats.** *Riker Laboratories, Inc. Experiment Number: 0680TR0008, December, 1980. AR-226 226-0016* US Environmental Protection Agency, Washington, DC, USA; 1980.
292. Wetzel LT: **Rat teratology study, T-3351, final report.** *Hazelton Laboratories America, Inc. Project Number: 154-160, December 19, 1983. US EPA AR-226 226-0014* 1983.
293. Case MT, York RG, Christian MS: **Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds.** *Int J Toxicol* 2001, **20**:101-109.
294. Yahia D, Tsukuba C, Yoshida M, Sato I, Tsuda S: **Neonatal death of mice treated with perfluorooctane sulfonate.** *J Toxicol Sci* 2008, **33**:219-226.
295. White SS, Calafat AM, Kuklenyik Z, Villaneuva LT, Zehr RD, Helfant L, Strynar MJ, Lindstrom AB, Thibodeaux JR, Wood C, Fenton SE: **Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring.** *Toxicol Sci* 2007, **96**:133-144.
296. Zheng L, Dong GH, Jin YH, He QC: **Immunotoxic changes associated with a 7-day oral exposure to perfluorooctanesulfonate (PFOS) in adult male C57BL/6 mice.** *Arch Toxicol* 2009, **83**:679-689.
297. Dong GH, Zhang YH, Zheng L, Liu W, Jin YH, He QC: **Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice.** *Arch Toxicol* 2009, **83**:805-815.
298. Qazi MR, Xia Z, Bogdanska J, Chang SC, Ehresman DJ, Butenhoff JL, Nelson BD, DePierre JW, Abedi-Valugerdi M: **The atrophy and changes in the cellular compositions of the thymus and spleen observed in mice subjected to short-term exposure to perfluorooctanesulfonate are high-dose phenomena mediated in part by peroxisome proliferator-activated receptor-alpha (PPAR alpha).** *Toxicology* 2009, **260**:68-76.
299. Lefebvre DE, Curran I, Armstrong C, Coady L, Parenteau M, Liston V, Barker M, Aziz S, Rutherford K, Bellon-Gagnon P, Shenton J, Mehta R, Bondy G: **Immunomodulatory effects of dietary potassium perfluorooctane sulfonate (PFOS) exposure in adult Sprague-Dawley rats.** *J Toxicol Environ Health A* 2008, **71**:1516-1525.
300. DeWitt JC, Copeland CB, Strynar MJ, Luebke RW: **Perfluorooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice.** *Environ Health Perspect* 2008, **116**:644-650.

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# Deriving environmental quality standards for perfluorooctanoic acid (PFOA) and related short chain perfluorinated alkyl acids

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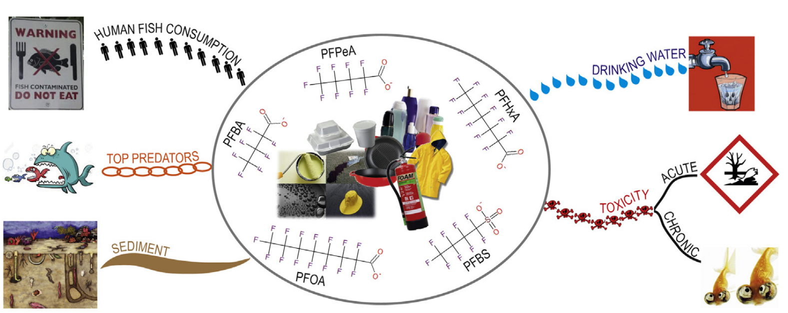
## HIGHLIGHTS

- Environmental Quality Standards (EQS) for selected perfluoroalkylacids are derived.
- For PFBA, PFPeA, PFHxA and PFBS the QS for drinking water are adopted as EQS.
- For PFOA the QS based on secondary poisoning of predators is adopted as EQS.
- 7, 3, 1, 3 and 0.1 $\mu g L^{-1}$ for PFBA, PFPeA, PFHxA, PFBS and PFOA are set as EQS.

## GRAPHICAL ABSTRACT

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## ABSTRACT

The evidence that in Northern Italy significant sources of perfluoroalkylacids (PFAA) are present induced the Italian government to establish a Working Group on Environmental Quality Standard (EQS) for PFAA in order to include some of them in the list of national specific pollutants for surface water monitoring according to the Water Framework Directive (2000/60/EC). The list of substances included perfluorooctanoate (PFOA) and related short chain PFAA such as perfluorobutanoate (PFBA), perfluoropentanoate (PFPeA), perfluorohexanoate (PFHxA) and perfluorobutanesulfonate (PFBS), which is a substitute of perfluorooctanesulfonate. For each of them a dossier collects available data on regulation, physico-chemical properties, emission and sources, occurrence, acute and chronic toxicity on aquatic species and mammals, including humans.

Quality standards (QS) were derived for the different protection objectives (pelagic and benthic communities, predators by secondary poisoning, human health via consumption of fishery products and water) according to the European guideline. The lowest QS is finally chosen as the relevant EQS. For PFOA a QS for biota was derived for protection from secondary poisoning and the corresponding QS

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for water was back-calculated, obtaining a freshwater EQS of 0.1 μg L$^{-1}$. For PFBA, PFPeA, PFHxA and PFBS threshold limits proposed for drinking waters were adopted as EQS.



## 1. Introduction

Because of their peculiar physical and chemical characteristics, perfluoroalkyl substance (PFAS) found wide application in several industrial processes and products such as surface treatment of textiles and paper, building paints, cosmetics, insecticide formulations, firefighting foams, and the production of fluoropolymer. Their characteristics such as resistance to hydrolysis, photolysis, microbial degradation make these substances highly persistent and widespread in all environmental compartments, especially water. PFAS include thousands of chemicals but environmental studies have mainly concentrated on perfluoroalkyl acids (PFAA) such as perfluoroalkylsulfonic acids (PFSA) and perfluoroalkylcarboxylic acids (PFCA). PFAA are low molecular weight surfactants in which all carbons are bonded to fluorine atoms, consisting of homologous series of molecules that differ in carbon chain length. The two PFAS most commonly used and found in the environment are perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA). They are widely employed in different industrial processes and their persistence in the environment associate with bioaccumulation in the trophic chain raising concern about the risks for consumers, including humans. Therefore the European Commission recently included PFOS in the list of priority substances, setting an Environmental Quality Standard (EQS) of 0.65 ng L$^{-1}$ for freshwater and 9.1 ng g$^{-1}$ for biota (Directive 2013/39/EC).

The hazard profile of PFOA is well known: PFOA is a persistent, bioaccumulative, and toxic (PBT) substance, which may cause severe and irreversible adverse effects on the environment and human health. PFOA has a harmonised classification in Annex VI of European Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) as Carc. 2, Repr. 1B and STOT RE 1 (liver). Due to its PBT and CMR properties, PFOA and its ammonium salt (APFO) have been identified as substances of very high concern (SVHC) under REACH by unanimous agreement between EU Member States in July 2013.

At the moment for PFOA, no limits have been established in the aquatic environment but only a provisional threshold for drinking waters was proposed by US Environmental Protection Agency (EPA) of 0.4 μg L$^{-1}$ (EPA, 2009). Shorter chain (<C7) homologues are currently tested and used as substitutes for PFOS and PFOA in industrial processes.

The evidence that in Northern Italy significant sources of PFAAs are present and surface and ground-waters are significantly impacted [2,3] induced the Italian government to establish a Working Group on Environmental Quality Standard (EQS) for PFAAs in order to include some of them in the list of national specific pollutants for surface water monitoring and derive their EQSs for water quality assessement in the context of the Water Framework Directive (2000/60/EC). EQSs should protect freshwater and marine ecosystems from possible short and long-term adverse effects of chemicals as well as human health via drinking water or ingestion of food originating from aquatic environments.

The PFFAs were chosen by considering the statistical distribution of concentrations and frequency of detection in the Italian surface and ground waters [3,4]. The list included the following substances: PFOA and related short chain (number of carbons <7) perfluorocarboxylate namely perfluorobutanoate (PFBA), perfluoropentanoate (PFPeA) and perfluorohexanoate (PFHxA). Perfluorobutanesulfonate (PFBS), which is a common substitute of PFOS, was considered too.

For each of them a dossier has been prepared which collects available data on regulation, physico-chemical properties, emission and sources, occurrence, acute and chronic toxicity on aquatic species and mammals, including humans.

This paper aims to present how EQSs for selected perfluoroalkylacids PFOA, PFBA, PFPeA, PFHxA and PFBS have been derived according to the European guidance document for derivation of EQSs under the Water Framework Directive [1]. By using the data in the dossiers, Quality Standards (QSs) were derived for different protection objectives based on: direct ecotoxicity to pelagic aquatic organisms; secondary poisoning of predators, human consumption of fishery products, human consumption of drinking water and to protect benthic (sediment-dwelling) species. Dossiers and proposed QSs were subject to a peer-reviewing process involving national experts of the Ministry of the Environment and international experts from other European Member States. After the reviewing process, the most protective QSs have been chosen as the national EQSs for the selected perfluoroalkylacids and adopted in the Italian legislation (Italian Legislative Decree 172/2015).

## 2. Methodology

EQSs were derived for PFOA and selected short chain perfluoroalkyl compounds PFBA, PFPeA, PFHxA and PFBS (referred to as SC-PFAA in the following text) in accordance with the European technical guidance document for derivation of environmental quality standards under the WFD (TGD-EQS) [1].

For each compound a dossier was compiled (Supplementary materials, SM1–SM5) according to the TGD-EQS format. This format requires regulatory information, physico-chemical data, occurrence in the different aquatic matrices, ecotoxicological data and toxicity data on mammals.

Toxicity data were collected from the scientific literature and from national and international databases. All available studies are summarised in the tables provided as Supplementary Materials (Tables SM7–SM9, with references in SM10). No toxicological data about invertebrates exposed to contaminated sediment have been found for the compounds under investigation.

The whole derived data set was properly assessed for reliability and relevance according to Klimisch et al. [5]. On this basis a selection and aggregation of the data were performed.

In order to cover both short- and long-term effects resulting from exposure, two water column EQSs is required: a short-term standard, referred to as a Maximum Allowable Concentration EQS (MAC-EQS) and a long-term standard, expressed as Annual Average Concentration EQS (AA-EQS). The MAC-EQS is based on information on direct ecotoxicological effects on aquatic organisms only. As AA-EQS is intended to protect the ecosystem, humans and predatory birds and mammals from long-term risks, it is defined as the lowest value among the derived QSs, calculated for the different protection objectives.

When the data were sufficient, the QSs were derived by probabilistic approach adopting Species Sensitivity Distribution (SSD) modelling. Otherwise, a deterministic approach was used applying appropriate assessment actors (AF) to the lowest reliable toxicity data.

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**Glossary**

AA-EQS$_{fw, eco}$ or AA-EQS$_{sw,eco}$ Annual Average Environmental Quality Standard in fresh or salt water [$\mu$g L$^{-1}$]
AA-QS$_{fw, eco}$ or AA-QS$_{sw,eco}$ QS based on direct ecotoxicity to pelagic organisms in fresh or salt water [$\mu$g L$^{-1}$]
ADI Acceptable Daily Intake [mg kg$_{bw}$$^{-1}$ d$^{-1}$]
AF Assessment Factor
AF$_{oral}$ Assessment Factor applied in extrapolation of QS$_{biota,secpois}$
BAF Bioaccumulation Factor [L kg$^{-1}$]
BCF Bioconcentration Factor [L kg$^{-1}$]
BMDL10 The lower limit of the 95% confidence interval of the benchmark dose for a 10% increase in effects [$\mu$g kg$_{bw}$$^{-1}$ d$^{-1}$]
BMF1 Biomagnification Factor of a simple food web that consists of water –BCF→ aquatic organisms –BMF1→ fish → fish-eating predator
BMF2 Biomagnification Factor of a marine simple food web that consists of water –BCF→ aquatic organisms –BMF1→ fish –BMF2→ fish-eating predator → top predator
bw Body weight [kg]
DFI Daily Food Intake [kg d$^{-1}$]
EQS Environmental Quality Standard
HC5 Hazardous concentration for 5% of the species (based on the SSD)
L(E)C50 One-half (50%) of the maximal Lethal (Effective) Concentration
LOAEL Lowest Observed Adverse Effect Levels [mg kg$_{bw}$$^{-1}$ d$^{-1}$]
MAC-QS$_{fw, eco}$ or MAC-QS$_{sw,eco}$ Maximum Allowable Concentration in fresh or salt water (short-term QS based on acute toxicity data) [$\mu$g L$^{-1}$]
NOAEL No Observed Adverse Effect Level [mg kg$_{bw}$$^{-1}$ d$^{-1}$]
NOEC No Observed Effect Concentration [$\mu$g L$^{-1}$ or $\mu$g kg$^{-1}$]
PFAA Perfluoroalkylacids
PFBA Perfluorobutanoate
PFBS Perfluorobutanesulfonate
PFHxA Perfluorohexanoate
PFOA Perfluorooctanoate
PFOS Perfluorooctanesulfonate
PFPeA Perfluoropentanoate
QC Quality Criteria
QS Quality Standard
QS$_{biota,hh}$ QS based on human consumption of fishery products [$\mu$g kg$^{-1}$]
QS$_{biota,secpois,fw}$ or QS$_{biota,secpois,sw}$ QS based on secondary poisoning of predators for freshwater or saltwater compartment [$\mu$g kg$^{-1}$]
QS$_{dw,hh}$ QS for human consumption of drinking water [$\mu$g L$^{-1}$]
QS$_{fw,secpois}$ or QS$_{sw,secpois}$ QS based on secondary poisoning converted into equivalent freshwater or saltwater concentration [$\mu$g L$^{-1}$]
QS$_{sed,fw}$ or QS$_{sed,sw}$ Sediment quality standard based on direct ecotoxicity to benthic (sediment dwelling) organisms in fresh or salt water [$\mu$g kg$^{-1}$]
SC-PFAA Short chain (number of carbon <7) perfluoroalkyl acids (PFBA, PFPeA, PFHxA, PFBS)
SSD Species Sensitivity Distribution model
TDI Tolerable Daily Intake [mg kg$_{bw}$$^{-1}$ d$^{-1}$]
TGD-EQS Technical Guidance for Deriving Environmental Quality Standards [1]
TL Threshold Level
TOX$_{oral}$ NOEC$_{oral,bird}$ or NOEC$_{oral,mammals}$ in kg kg$_{food(fw)}$$^{-1}$
WFD Water Framework Directive (2000/60/EC)

The QSs for SC-PFAAs were determined using the deterministic approach. Only for PFOA the acute toxicity data were sufficient for statistical extrapolation of QS by implementing the SSD approach.

## 3. Results and discussion

### 3.1. Toxicity data

Among the compounds of interest the largest dataset has been collected for PFOA, which includes both acute and chronic toxicity tests on organisms exposed to water and toxicity test on mammals and birds (Tables 1 and 4, SM7, SM8 and SM9).

For the other short chain perfluoroalkyl acids, data set is much more limited. Acute toxicity data on aquatic organisms are available for all the SC-PFAA (Table 2, Table 3 and SM7) but chronic toxicity data to aquatic organisms are available only for PFBS (Table 4 and SM8). In the case of PFHxA the number of reliable data is insufficient to derive a consistent quality standard for pelagic organisms.

Few toxicity studies on mammalian diet and oral exposure are reported for PFBA, PFHxA and PFBS and only one mammalian toxicity study was found for PFPeA (SM9). For PFBA, PFPeA and PFHxA the number of studies is insufficient to derive a reliable QS$_{biota,secpois}$. However indicative values of the biota standards for PFBA and PFHxA are derived based on the lowest NOAEL/LOAEL available.

Saltwater ecotoxicity data are scarce and insufficient to enable a statistical comparison of the freshwater and saltwater data and to define marine quality standards based only on saltwater toxicity values. The available data, however, do not point out a difference in sensitivity, therefore, according to TGD-EQS [1], the freshwater and saltwater data are combined and separate QSs for all selected PFAAs were derived for freshwater and saltwater environments using different assessment factors (TGD-EQS). This is consistent with the provisions of REACH for marine effects assessment where a larger AF is recommended to cover the increased uncertainty resulting from the larger diversity of marine ecosystems and the limited availability of effects data for marine life forms. No toxicological data of invertebrates exposed to contaminated sediment were available for any examined compound.

### 3.2. Derivation of QS from direct toxicity in the water column

#### 3.2.1. MAC-QS$_{water,eco}$ for PFOA

Short term or acute toxicity tests are used to derive a Maximum Acceptable Concentration-QS (Table 1). Short term toxicity PFOA dataset contains reliable L(E)C50 values from 24 different species covering 8 taxonomic groups (including algae, crustacean, rotifers, insect, annelids, echinodermata, amphibian and fish). The range of taxonomic groups covered and the number of L(E)C50 values from different species fulfil the TGD-EQS requirements for the use of the SSD to derive the MAC-QS. Acute toxicity data have been aggregated to one toxicity value per species, unreliable tests [5] were excluded from elaboration and SSD generator V$_{1-12}$ [6] has been used to calculate the hazardous concentration for 5% of species (HC5). Details on data selection and SSD elaboration are reported in Supplementary Materials (Table SM6, with references in SM10). The estimated

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**Table 1**
PFOA acute aquatic toxicity (The full dataset is available in Table SM7, with references in SM10).

| | Species | Exp time | Endpoint | LC50 (95% CI) mg $L^{-1}$ | EC50 (95% CI) mg $L^{-1}$ | References |
|---|---|---|---|---|---|---|
| Freshwater | | | | | | |
| Cyanobacteria | *Geitlerinema amphibium* | 72 h | biomass[a] | | $247.8 \pm 12.4$[b] | [45] |
| | *Anabaena* CPB4337 | 24 h | luminescence inhibition | | 19.81 (15.44–26.44) | [46] |
| Algae | *Pseudochirchneriella subcapitata* | 72 h | growth rate and biomass | | >100 | [47] |
| | | 96 h | | | >100 | |
| | *Pseudochirchneriella subcapitata* | 72 h | growth rate and biomass | | >400 | [11] |
| | | 96 h | | | >400 | |
| | *Pseudochirchneriella subcapitata* | 72 h | growth inibition (biomass) | | 96.2 (88.6–113.7) | [48] |
| | *Pseudokirchneriella subcapitata* | 4.5 h | photosynthesis | | 746.40 (726.99–768.29) | [49] |
| | *Scenedesmus quadricanda* | 96 h | not reported | | 269.63 (207.83–349.82) | [50] |
| | *Chlamydomonas reinhardtii* | 96 h | growth inhibition | | $51.9 \pm 1.0$ | [51] |
| | *Scenedesmus obliquus* | 96 h | growth inhibition | | $44.0 \pm 1.5$ | [51] |
| | *Chlorella vulgaris* | 72 h | biomass[a] | | $974.82 \pm 49.56$[b] | [45] |
| Invertebrata: Crustacean | *Daphnia magna* | 48 h | immobilization | | 480 | [11] |
| | *Daphnia magna* | 48 h | immobilization | | 480 | [47] |
| | *Daphnia magna* | 24 h | immobilization | | 675.05 (559.62–790.50) | [52] |
| | | 48 h | | | 476.52 (375.32–577.72) | |
| | *Daphnia magna* | 24 h | immobilization | | 219.33 (209.01–229.25) | [53] |
| | | 48 h | | | 211.07 (184.22–254.86) | |
| | *Chydorus sphaericus* | 24 h | immobilization | | 175.96 (92.11–221.81) | |
| | | 48 h | | | 116.48 (50.39–142.51) | |
| | *Moina macrocopa* | 24 h | immobilization | | 348.76 (272.65–424.87) | [52] |
| | | 48 h | | | 199.51 (153.89–245.13) | |
| | *Daphnia magna* | 48 h | mortality | 201.85 (134.68–302.50) | | [50] |
| | *Daphnia magna* | 24 h | immobilization | | 298 (278–321) | [54] |
| | | 48 h | | | 181 (166–198) | |
| | *Neocaridina denticulate* (green neon shrimp) | 24h | mortality | >1000 | | [54] |
| | | 48 h | | 712(663–764) | | |
| | | 72 h | | 546 (502–594) | | |
| | | 96 h | | 454 (418–494) | | |
| | *Macrobrachium nipponense* (freshwater shrimp) | 96 h | mortality | 366.66 (253.09–531.18) | | [50] |
| Invertebrata: Rotifers | *Brachionus calyciflorus* | 24 h | mortality | 150 | | [55] |

Table 1 (*Continued*)

| | Species | Exp time | Endpoint | LC50 (95% CI) mg $L^{-1}$ | EC50 (95% CI) mg $L^{-1}$ | References |
|---|---|---|---|---|---|---|
| Invertebrata: Gastropoda | *Physa acuta* | 24 h | mortality | 856 (768–954) | | [54] |
| | | 48 h | | 732 (688–779) | | |
| | | 72 h | | 697 (661–735) | | |
| | | 96 h | | 672 (635–711) | | |
| | *Cipangopaludina cathayensis* | 96 h | mortality | 740.07 (597.66–916.41) | | [50] |
| Invertebrata: Platyhelminthes | *Dugesia japonica* | 24 h | mortality | 352 (331–374) | | [54] |
| | | 48 h | | 345 (325–366) | | |
| | | 72 h | | 343 (324–364) | | |
| | | 96 h | | 337 (318–357) | | |
| Invertebrata: Insecta | *Chironomus plumosus* | 96 h | mortality | 402.24 (323.83–499.63) | | [50] |
| Invertebrata: Anellida | *Limnodrilus hoffmeisteri* | 96 h | mortality | 568.20 (476.33–677.80) | | [50] |
| Vertebrata: Amphibia | *Bufo gargarizans* | 96 h | mortality | 114.74 (83.02–158.58) | | [50] |
| Vertebrata: Fish | *Pseudorasbora parva* | 96 h | mortality | 365.02 (269.78–493.86) | | [50] |
| | *Carassius auratus* | 96 h | mortality | 606.61 (460.93–798.32) | | [50] |
| | *Oncorhynchus mykiss* (rainbow trout) | 96 h | mortality | 707 | | [11] |
| | *Oncorhynchus mykiss* (rainbow trout) | 96 h | mortality | 800 | | [11] |
| | *Danio rerio* (zebrafish embryo test) | 144 hpf | mortality | 430 (290–710) | | [56] |
| | | | mortality and malformation effects | | 350 (290–430) | |
| | *Danio rerio* (zebrafish embryo test) | 96 hpf | mortality and malformation effects[c] | >500 | 205.72(168.25–251.53) | [57] |
| | | 120 hpf | | >500 | 113.05 (96.22–132.84) | |
| Marine water | | | | | | |
| Bacteria | *Vibrio fischeri* | *30 min* | luminescence inhibition | | 570.19 ± 57.33 | [58] |
| | *Vibrio fischeri* | 15 min | luminescence inhibition | | 524 (505–538) | [48] |
| | *Photobaterium phosphoreum* | 15 min | luminescence inhibition | | 14.65 | [7] |
| Algae | *Skeletonema marinoi* | 72 h | biomass[a] | | 367.52 ± 16.5[b] | [45] |
| | *Isochrysis galbana* | 72 h | growth inhibition | | 163.6 (131.7–203.2) | [59] |
| Invertebrata: Crustacea | *Siriella armata* | 96 h | mortality | 15.5 (13.0–18.6) | | [59] |
| Invertebrata: Echinodermata | *Paracentrotus lividus* | 48 h | growth inhibition | | 110.0 (99.2–121.9) | [59] |
| Vertebrata: Fish | *Psetta maxima* | 144 h | abnormalities/mortality | 11.9 (9.5–14.9) | | [59] |

*Notes*: hpf: hours post fertilization.
[a] biomass assessed by optical density.
[b] standard deviation.
[c] malformation of head and tail and effects on growth.

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**Table 2**
PFBA, PFPeA, PFHxA acute aquatic toxicity (The full dataset is available in Table SM7, with references in SM10).

| | Species | Exp time | Endpoint | LC50 (95% CI) mg $L^{-1}$ | EC50 (95% CI) mg $L^{-1}$ | References |
|---|---|---|---|---|---|---|
| Freshwater | | | | | | |
| PFBA | | | | | | |
| Algae | *Pseudokirchneriella subcapitata* | 4.5 h | photosynthesis | | 260.96 (213.03–319.55)[a] | [49] |
| Invertebrata: Crustacean | *Dapnia magna* | 24 h | immobilization | | 184.27 (182.78–185.55)[a] | [53] |
| | | | | | >4260.6[b] | |
| | | 48 h | | | 180.65 (179.15–182.35)[a] | |
| | | | | | >4260.6[b] | |
| | *Chydorus sphaericus* | 24 h | immobilization | | 534.49 (513.19–555.37)[a] | [53] |
| | | | | | >4.26[b] | |
| | | 48 h | | | 460.14 (440.97–479.10)[a] | |
| | | | | | >4260.6[b] | |
| Invertebrata: Rotifera | *Brachionus calyciflorus* | 24 h | mortality | 110[a] | | [8] |
| Vertebrata: Fish | *Danio rerio* | 144 hpf | mortality | >3000[a] | | [56] |
| | | | mortality and malformation effects | | >2200 (1200–22,000)[a,d] | |
| | *Danio rerio* | 96 hpf | mortality and malformation effects[e] | >3000[b] | | [57] |
| | | 120 hpf | | >3000[b] | | |
| PFPeA | | | | | | |
| Algae | *Pseudokirchneriella subcapitata* | 72 h | biomass | | 81.7 (76.7–87.5) | [9] |
| Invertebrata: Crustacean | *Daphnia magna* | 48 h | immobilization | | >112 | [9] |
| Invertebrata: Rotifera | *Brachionus calyciflorus* | 24 h | mortality | 130 | | [8] |
| Vertebrata: Fish | *Pimephales promelas* | 96 h | mortality | 31.8 (10.3–98.3) | | [9] |
| PFHxA | | | | | | |
| Algae | *Pseudokirchneriella subcapitata* | 72 h | biomass | >100 | | [9] |
| Invertebrata: Rotifera | *Brachionus calyciflorus* | 24 h | mortality | 140 | | [8] |
| Invertebrata: Crustacea | *Daphnia magna* | 48 h | mortality | >96.5 | | [9] |
| Vertebrata: Fish | *Oncorhynchus mykiss* | 96 h | mortality | >99.2 | | [9] |
| Marine water | | | | | | |
| PFBA | | | | | | |
| Bacteria | *Photobacterium phosphoreum* | 15 min | luminescence inhibition | | 14.07 | [7] |
| PFPeA | | | | | | |
| Bacteria | *Photobacterium phosphoreum* | 15 min | luminescence inhibition | | 16.22 | [7] |
| PFHxA | | | | | | |
| Bacteria | *Vibrio fischeri* | 30 min | luminescence inhibition | | 1335.39 ± 123.18 | [58] |
| | *Photobacterium phosphoreum* | 15 min | luminescence inhibition | | 17.20 | [7] |
| Cyanobacteria | *Geitlerinema amphibium* | 72 h | biomass[f] | | 995.49 ± 50.09[c] | [45] |
| Algae | *Chlorella vulgaris* | 72 h | biomass[f] | | 4019.51 ± 200.35[c] | [45] |
| | *Skeletonema marinoi* | 72 h | biomass[f] | | 1477.58 ± 72.00[c] | [45] |

*Notes*: hpf: hours post fertilization.
[a] test without pH adjustament.
[b] test with pH adjustment.
[c] standard deviation.
[d] values based on combined sublethal and lethal embryotoxicity effect data.
[e] malformation of head and tail and effects on growth.
[f] biomass assessed by optical density.

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**Table 3**
PFBS acute aquatic toxicity (The full dataset is available in Table SM7, with references in SM10).

| | Species | Exp time | Endpoint | LC50 (95% CI) mg $L^{-1}$ | EC50 (95% CI) mg $L^{-1}$ | References |
|---|---|---|---|---|---|---|
| Freshwater | | | | | | |
| Sewage microorganisms | | 3 h | respiration inhibition | | >1000 | [10] |
| Cyanobacteria | *Anabaena* CPB4337 | 30 min | bioluminescence inhibition | | 8386 (7752–8693) | [48] |
| Algae | *Pseudokirchneriella subcapitata* | 72 h | growth inhibition (biomass) | | >20250 (37% growth inhibition at 20,250 mg $L^{-1}$) | [48] |
| | *Pseudokirchneriella subcapitata* | 96 h | growth inhibition | | 5733 (5659–5817) | [10] |
| | | | biomass | | 2347 (2018–2707) | |
| Invertebrata: Crustacea | *Daphnia magna* | 48 h | immobilization | | 2183 (1707–3767) | [10] |
| Vertebrata: Fish | *Danio rerio* | 144 hpf | mortality and malformation effects[a] | 1500 (1100–1900) | 450 (350–600)[b] | [56] |
| | *Danio rerio* | 96 hpf | mortality and malformation effects[a] | >3000 | 1900.78 (1728.76–2089.92)[b] | [57] |
| | | 120 hpf | | >3000 | 1592.32 (1316.19–1776.96)[b] | |
| | *Pimephales promelas* (fathead minnow)[c] | 96 h | mortality | 1938 (888–3341) | | [10] |
| | *Lepomis macrochirus* (bluegill sunfish)[d] | 96 h | mortality | 6452 | | [10] |
| Marine water | | | | | | |
| Bacteria | *Vibrio fischeri* | 15 min | bioluminescence inhibition | | 17,520 (16,850–18,200) | [48] |
| Invertebrata: Crustacea | *Mysidopsis bahia* (mysid shrimp) | 96 h | mortality and abnormal behaviour | | 372 (314–440) | [10] |

Notes: hpf: hours post fertilization.
[a] malformation of head and tail and effects on growth.
[b] values based on combined sublethal and lethal embryotoxicity effect data.
[c] juveniles 35 ± 5 mm and mean wet weight 320 ± 100 mg.
[d] juveniles 44 ± 10 mm and mean wet weight 1000 ± 600 mg.

median of the HC5 is 22.2 mg $L^{-1}$. To take into account the residual uncertainty, a default assessment factor of 10 is applied and an MAC-QS for the freshwater environment of 2.22 mg $L^{-1}$ is derived (Table 5).

Short-term L(E)C50 are available for marine algae, crustacea and fish and only one additional short-term toxicity data from a specific saltwater taxonomic group (Echinodermata) is available. In this situation HC5 calculated from the combined dataset is used to derive the $QS_{sw,eco}$ applying an additional AF of 5 was used, giving an MAC-QS for the marine environment of 0.450 mg $L^{-1}$ (Table 5).

### 3.2.2. MAC-$QS_{water,eco}$ for SC-PFAA

Short-term toxicity data are available for five taxonomic groups (bacteria, algae, plant, crustaceans, rotifers and fish) for PFBA, PFPeA and PFHxA and only for four taxonomic groups (bacteria, algae, crustaceans and fish) for PFBS. Though the acute base set (algae, Daphnia, fish) is complete, the range of taxonomic groups covered is insufficient to enable the use of SSD to derive the MAC-QS. Therefore, the assessment factor approach has been used for all the SC-PFAAs.

The TGD-EQS [1] recommend that, when there are at least 3 short-term tests of species from three trophic levels of the base set (algae, Daphnia, fish) and the standard deviation (SD) of the log transformed acute toxicity data is <0.5, the MAC-$QS_{fw,eco}$ is derived by applying an assessment factor of 10 to the lowest L(E)C50. Conversely, when the log transformed acute toxicity data SD is >0.5 the MAC-$QS_{fw,eco}$ is derived by applying an assessment factor of 100 to the lowest L(E)C50. According to TGD-EQS, if no data for an additional marine taxonomic group are available, combined toxicity data are used to derive the MAC-$QS_{sw,eco}$ by applying an additional AF of 10 to the MAC-$QS_{fw,eco}$.

The lowest acute toxicity concentrations for PFBA, PFPeA and PFHxA were obtained for the bioluminescence inhibition of the *Photobacterium phosphoreum* [7]. However this study was considered not reliable and excluded because its documentation is lacking. Furthermore there is no international agreement upon these methods and, on the consequence, these data would not be acceptable for use in ECHA dossiers.

From the reliable dataset for PFBA, the study on the freshwater invertebrate *Brachionus calyciflorus* (24 h LC50: 110 mg $L^{-1}$) [8] has been chosen as the key driving study for MAC-QS setting. The SD of the log transformed acute toxicity data is >0.5. By applying an AF of 100 to the lowest acute effect concentration of 110 mg $L^{-1}$ an MAC-QS for the freshwater environment of 1.1 mg $L^{-1}$ is derived (Table 5). Because no data for an additional marine taxonomic group are available, an MAC-$QS_{sw,eco}$ for the marine environment of 0.110 mg $L^{-1}$ is derived (Table 5).

For PFPeA the SD of the log transformed acute toxicity data is <0.5. The study on the freshwater fish *Pimephales promelas* [9] is considered reliable without restriction and the 96 h LC50 (31.8 mg $L^{-1}$) is used to derive the MAC-QS by applying an AF of 10, obtaining a MAC-QS for the freshwater environment of 3.18 mg $L^{-1}$

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**Table 4**
PFOA and PFBS chronic aquatic toxicity (The full dataset is available in Table SM8, with references in SM10).

| | Species | Exp time | Endpoint | EC10 (95% CI) mg $L^{-1}$ | NOEC mg $L^{-1}$ | References |
|---|---|---|---|---|---|---|
| Freshwater | | | | | | |
| PFOA | | | | | | |
| Algae | *Pseudochirchneriella subcapitata* | 72 h | growth rate and biomass | | 200 | [47] |
| | | 96 h | | | 12.5 | |
| | *Pseudochirchneriella subcapitata* | 72 h | growth rate and biomass | | 200 | [11] |
| | | 96 h | | | 12.5 | |
| | *Pseudokirchneriella subcapitata* | 4.5 h | photosynthesis | | 413.06 | [49] |
| Aquatic Plant | *Myriophyllum spicatum* | 35 d | growth (plant length) | 31.5 (0–68.2) | 23.9 | [60] |
| | | | root number | 10.2 (6.6–13.7) | 23.9 | |
| | | | root length | 8.8 (5.9–11.7) | 23.9 | |
| | | | longest root | 24.3 (0–56.7) | 23.9 | |
| | | | node number | 8.3 (5.3–11.4) | 23.9 | |
| | | | biomass (wet mass) | 22.8 (0–53.5) | 74.1 | |
| | | | biomass (dry mass) | 19.7 (0–53.5) | 74.1 | |
| | *Myriophyllum sibiricum* | 35 d | growth (plant length) | 23.7 (5.3–42.1) | 23.9 | [60] |
| | | | root number | 29.2 (0–69.2) | 23.9 | |
| | | | root length | 24.8 (0–64.1) | 23.9 | |
| | | | longest root | 30.0 (0–90.6) | 23.9 | |
| | | | node number | 7.8 (6.0–9.7) | 23.9 | |
| | | | biomass (wet mass) | 21.6 (0–59.07) | 23.9 | |
| | | | biomass (dry mass) | 24.7 (0–340.7) | 23.9 | |
| Invertebrata: Crustacea | *Daphnia magna* | 21 d | reproduction | | NR | [47] |
| | | | growth (as length) | | 44.2 | |
| | *Daphnia magna* | 21 d | reproduction | | 12.5 | [52] |
| | *Moina macrocopa* | 7 d | reproduction | | 3.125 | [52] |
| | *Daphnia magna* | 21 d | survival | | >100 | [61] |
| | | | reproduction | | 10 | |
| | *Daphnia magna* | 21 d | reproduction | | 20 | [11] |
| | | | growth (as length) | | 44.2 | |
| | *Daphnia magna* | 21 d | reproduction rate | | 22 | [11] |
| | | 14 d | reproduction | | 8 | |
| | | | survival | | 60 | |
| | *Daphnia magna* | 21 d | survival | 11.12 | | [50] |
| | | | reproduction | 7.02 | | |
| Vertebrata: Amphibia | *Bufo gargarizans* | 30 d | survival | 5.89 | | [50] |
| Vertebrata: Fish | *Oncorhynchus mykiss* (rainbow trout)[a,b] | 85 d | mortality | | 40[c] | [49] |
| | *Oncorhynchus mykiss* (rainbow trout)[a,b] | 85 d | mortality and growth (length) | | 40[c] | [11] |
| | *Pimephales promelas* | 39 d | survival | | >74.1[d] | [11] |
| | | | time for first oviposition | | 50[d] | |
| | | | male plasma 11-ketotestosterone and testosterone | | 0.3[d] | |
| | *Pimephales promelas*[e] | 30 d | hatchability, survival growth and histopathology | | >100 | [11] |
| | *Pseudorasbora parva* | 30 d | survival | 11.78 | | [50] |
| PFBS | | | | | | |
| Algae | *Pseudokirchneriella subcapitata* | 96 h | growth inhibition | | 1077 | [10] |
| | | | biomass | | 1077 | |
| Invertebrata: Crustacea | *Daphnia magna* | 21 d | reproduction/length | | 502 | [10] |
| Marine water | | | | | | |
| PFOA | | | | | | |
| Algae | *Isochrysis galbana* | 72 h | growth inhibition | 41.6 (25.9–66.6) | 25 | [59] |

*Notes*:
[a] embryos.
[b] larvae and juveniles.
[c] for all life stages.
[d] real concentrations applied to mesocosm.
[e] eggs and fry.

(Table 5). Because no data for an additional marine taxonomic group are available, a MAC-$QS_{sw,eco}$ for the marine environment of 0.318 mg $L^{-1}$ is derived (Table 5).

The lowest acute toxicity concentration is 140 mg $L^{-1}$ (24 h LC50, *Brachionus calyciflorus*, [8]). The toxicity studies reported by [9] for PFHxA were not sufficiently documented and the toxicity values, which are maximum effect concentrations, cannot be used for QS derivation. Because three major taxonomic groups −Cyanobacteria, algae, and Rotifera-, but only two trophic levels are available, it is not possible to derive a consistent quality standard.

The lowest acute toxicity value for PFBS (96 h EC50 = 372 mg $L^{-1}$) has been obtained for the crustacean *Mysidopsis bahia* [10] and the study has been considered reliable without restriction. The SD of the log transformed acute toxicity data is >0.5. By applying an AF of 100 to the lowest acute effect concentration an MAC-QS for the freshwater environment of 3.72 mg $L^{-1}$ is derived (Table 5). *Mysidopsis bahia* is the only marine species represented in the data-set, since the *Vibrio* test is regarded as unreliable. In this situation the combined toxicity data can be used to derive the $QS_{sw,eco}$ and an additional factor of 10 is applied for saltwater, giving an MAC-QS for the marine environment of 0.372 mg $L^{-1}$ (Table 5).

### 3.2.3. *AA-$QS_{water,eco}$ for PFOA*

Long term toxicological data are available for five taxonomic groups including algae, plant, crustaceans, fish and amphibians together with a mesocosm study [11] (Table 4). No toxicological

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