Perfluorooctanoic acid (PFOA) and Its Salts and Transformation and Degradation Precursors

Perfluorooctanoic acid (PFOA, C8) and its salts are perfluorinated organic compounds with surfactant properties. PFOA can be released from several fluorochemicals, such as fluorinated telomere alcohols and other precursor compounds of fluorinated polymers by biotic and /or metabolic decomposition. PFOA and its salts are used in a variety of industrial applications, such as plasticizers, lubricants, wetting agents, and emulsifiers. They are used in the manufacture of fluoroelastomers and fluoropolymers, such as polytetrafluoroethylene (Teflon) and polyvinylidine fluoride. These are used as protective finishes to make non-stick cookware and water and stain repelling treatments for carpets, furniture upholstery and textiles. Fluoroelastomers and fluoropolymers are also used in the automotive, mechanical, aerospace, chemicals, electrical, medical, and building/construction industries. Uses in consumer products include coatings on paper, textiles, and carpet, personal care products, and nonstick coatings on cookware.

Biomonitoring studies indicate widespread exposure of the population to PFOA. PFOA can cross the placenta and accumulate in amniotic fluid. It has also been measured in cord blood from newborns. PFOA is persistent in the environment. The general population is exposed through the use of products containing PFOA and its salts and transformation and degradation precursors, and through environmental exposures, and occupational exposures occur in workplaces were these chemicals are manufactured and used.

PFOA and its salts and transformation and degradation precursors passed the animal data screen, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

- Retrospective occupational cohort mortality studies
    - Workers at 3M Cottage Grove, Minnesota plant where APFO production occurred: Gilliland and Mandel (1993); U.S. EPA (2005, pp. 13-16).
    - Workers at a perfluorooctanesulphonyl fluoride-based fluorochemicals production facility, with likely exposure to multiple fluorochemicals, including PFOA: Alexander *et al.* (2003), Alexander and Olsen (2007)
    - Workers Dupont's Washington Works plant in Parkersburg, West Virginia: U.S. EPA (2005, p. 16)

Animal carcinogenicity data

- Long-term diet studies in rats
  - Two-year studies in male and female Sprague-Dawley rats: Sibinski (1987), as described in U.S. EPA (2005, pp. 55-58)
  - Two year study in male Sprague-Dawley rats: Cook *et al*. (1994) as fully described in Biegel *et al*. (2001); described in U.S. EPA (2005, p. 58)

- Tumor promotion studies
  - Male Wistar rats (initiation-selection-PFOA promotion protocol, seven month study duration): Abdellatif *et al*. (1990); Nilsson *et al*. (1991)
  - Rainbow trout: Tilton *et al*. (2008)

Other relevant data

- Genotoxicity
  - Review: U.S. EPA (2005, p. 47)
  - Micronuclei in the human hepatoma cell line HepG2: Yao and Zhong (2005)
  - DNA strand breaks in the human hepatoma cell line HepG2: Yao and Zhong (2005)
  - 8-hydroxydeoxyguanosine in the human hepatoma cell line HepG2: Yao and Zhong (2005)

- Hormonal effects
  - Studies in Saccharomyces cervisiae: Ishibashi *et al*. (2007)
  - Studies in freshwater male tilapia hepatocyte cultures: Liu *et al*. (2007)
  - Studies in MCF-7 breast cancer cells: Maras *et al*. (2006)
  - Studies in male CD rats: Cook *et al*. (1992); Liu *et al.* (1996)
  - Studies in peripubertal mice: Yang *et al*. (2008)
  - Studies in male workers: Olsen *et al*. (1998)

- Immune system effects
  - Review: U.S. EPA (2005, pp. 59-60)
  - Studies in mice: DeWitt *et al.* (2008); Son *et al*. (2008); Yang *et al*. (2000)

- Inhibition of gap junctional intercellular communication
  - Studies in WB-rat liver epithelial cells: Upham *et al*. (1998)

- Toxicogenomic studies
  - Studies in rare minnow liver: Wei *et al.* (2008a, b)
  - Studies in rainbow trout liver: Tilton *et al.* (2008)

- Studies in wild-type and PPARα-mull mouse liver: Rosen *et al*. (2008a, b)
- Studies in male Sprague-Dawley rat liver: Martin *et al.* (2007)

- Mechanisms
  - Peroxisome proliferator-activated receptor α (PPARα) agonism: Wolf *et al.* (2008), Ito *et al*. (2007), Takashima *et al.* (2008), Yang *et al.* (2007),
  - Disruption of the hypothalamic-pituitary-gonad axis: Cook *et al.* (1992)
  - Review: U.S. EPA (2005, pp. 75-84)

Reviews

- U.S EPA (2005)

- Lau *et al.* (2007)

References[1]

Abdellatif AG, Préat V, Vamecq J, Nilsson R, Roberfroid M (1990). Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,4-dichlorophenoxyacetic acid, 2,4,5,-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin. *Carcinogenesis* **11**:1899-1902.

Alexander BH, Olsen GW (2007). Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. *Ann Epidemiol* **17**:471-478.

Alexander BH, Olsen GW, Burris JM, Mandel JH, Mandel JS (2003). Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Environ Med* **60**:722-9.

Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook, JC (2001). Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol Sci* **60**:44-55.

Cook JC, Murray SM, Frame SR, Hurt ME (1992). Induction of Leydig cell adenomas by ammonium perfluorooctanote: A possible endocrine -related mechanism. *Toxicol Applied Pharmacol* **113**:209-217.

DeWitt J, Copeland CB, Strynar MJ, Luebke RW (2008). Perfluorooctanoic acid - induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environ Health Perspect* **116:**644-650.

[1] Copies of these listed references, as either the abstract, the relevant sections of the publication, or the complete publication, have been provided to members of the Carcinogen Identification Committee. These references have been provided in the order in which they are discussed in this document.

Gilliland FD, Mandel JS (1993). Mortality among employees of a perfluorooctanoic acid production plant. *J Occup Med* **35**:950-4.

Ishibashi H, Ishida H, Matsuoka M, Tominaga N, Arizono K (2007). Estrogenic effects of fluorotelomer alcohols for human estrogen receptor isoforms α and β *in vitro*. *Biol Pharm Bull* **30**:1358-1359.

Ito Y, Yamanoshita O, Asaeda N, Tagawa Y, Lee C-H, Aoyama T, Ichihara G, Furuhashi K, Kamijima M, Gonzalez FJ, Nakajima T (2007). Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. *J Occup Health* **49**:172-182.

Lau C, Anitole K, Hodes, C, Lai D, Pfahles-Hutchens A, Seed J (2007). Perfluoroalkyl Acids: A Review of monitoring and toxicological findings. *Toxicol Sci* **99**:366-394.

Liu RCM, Hurtt ME, Cook JC, Biegel LB (1996). Effect of the peroxisome proliferator, ammonium perfluorooctanoate (C8), on hepatic aromatase activity in adult male Crl:CD BR (CD) rats. *Fund Appl Toxicol* **30**:220-228.

Liu C, Du Y, Zhou B (2007). Evaluation of estrogenic activities and mechanism of action of perfluorinated chemicals determined by vitellogenin induction in primary cultured tilapia hepatocytes. *Aquat Toxicol* **85**:267-77.

Maras M, Vanparys C, Muylle F, Robbens J, Berger U, Barber JL, Blust R, De Coen W (2006). Estrogen-like properties of fluorotelomer alcohols as revealed by mcf-7 breast cancer cell proliferation. *Environ Health Perspect* **114**:100-5.

Martin MT, Brennan RJ, Hu W, Ayanoglu E, Lau C, Ren H, Wood CR, Corton JC, Kavlock RJ, Dix DJ (2007). Toxicogenomic study of triazole fungicides and perfluoroalkyl acids in rat livers predicts toxicity and categorizes chemicals based on mechanisms of toxicity. *Toxicol Sci* **97**:595-613.

Nilsson R, Beije B, Préat V, Erixon K, Ramel C (1991). On the mechanism of the hepatocarcinogenicity of peroxisome proliferators. *Chem Biol Interact* **78**:235-50.

Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH (1998). An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanonic acid. *J Occup Environ Med* **40**:614-622.

Rosen MB, Lee JS, Ren H, Vallanat B, Liu J, Waalkes MP, Abbott BD, Lau C, Corton JC (2008a). Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: evidence for the involvement of nuclear receptors PPAR alpha and CAR. *Toxicol Sci* **103**:46-56.

Rosen MB, Abbott BD, Wolf DC, Corton JC, Wood CR, Schmid JE, Das KP, Zehr RD, Blair ET, Lau C (2008b). Gene profiling in the livers of wild-type and PPARalpha-null mice exposed to perfluorooctanoic acid. *Toxicol Pathol* **36**:592-607.

Son HY, Lee S, Tak EN, Cho HS, Shin HI, Kim SH, Yang JH (2008). Perfluorooctanoic acid alters T lymphocyte phenotypes and cytokine expression in mice. *Environ Toxicol* Dec 2 [Epug ahead of print].

Takashima K, Ito Y, Gonzalez FJ, Nakajima T (2008). Different mechanisms of DEHP-induced hepatocellular adenoma tumorigenesis in wild-type and *Pparα*-null mice. *J Occup Health* **50**:169-80.

Tilton SC, Orner GA, Benninghoff AD, Carpenter HM, Hendricks JD, Pereira CB, Williams DE (2008). Genomic profiling reveals an alternative mechanism for hepatic tumor promotion by perfluorooctanoic acid in rainbow trout. *Environ Health Perspect* **116**:1047-1055.

Upham BL, Deocampo ND, Wurl B, Trosko JE (1998). Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. *Int J Cancer* **78**:491-5.

U.S. Environmental Protection Agency (U.S. EPA, 2005). SAB Review Draft. Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and Its Salts. U.S. EPA, Office of Pollution Prevention and Toxics, Risk Assessment Division January 4, 2005.

Wei Y, Chan LL, Wang D, Zhang H, Wang J, Dai J (2008a). Proteomic analysis of hepatic protein profiles in rare minnow (Gobiocypris rarus) exposed to perfluorooctanoic acid. *J Proteome Res* **7:**1729-39.

Wei Y, Liu Y, Wang J, Tao Y, Dai J (2008b). Toxicogenomic analysis of the hepatic effects of perfluorooctanoic acid on rare minnows (Gobiocypris rarus). *Toxicol Appl Pharmacol* **226:**285-97.

Wolf DC, Moore T, Abbott BD, Rosen MB, Das KP, Zehr RD, Lindstrom AB, Strynar MJ, Lau C (2008). Comparative hepatic effects of perfluorooctanoic acid and WY 14,643 in PPAR-alpha knockout and wild-type mice. *Toxicol Pathol* **36**:632-9.

Yang Q, Ito S, Gonzalez FJ (2007). Hepatocyte-restricted constitutive activation of PPARα induces hepatoproliferation but not hepatocarcinogenesis. *Carcinogenesis* **28**:1171-1177.

Yang C, Tan YS, Harkema JR, Haslam SZ (2008). Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. *Reprod Toxicol* Nov. 1 [Epub ahead of print]

Yang Q, Xie Y, Depierre JW (2000). Effects of peroxisome proliferators on the thymus and spleen of mice. *Clin Exp Immunol* **122**:219-26.

Yao X, Zhong L (2005). Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanoic acid. *Mutat Res* **587:**38-44.