



Effects found in critical PFOA laboratory studies (see more detailed version – page 1 of 2)

Rat reproduction study¹	
<p>0 mg/kg/d Female: < 5.3 ppb blood Male: 34.4 ppb</p>	
<p>1 mg/kg/d* Female: not measured, estimated to be 40 ppb Male: not measured, not estimated because serum dose response not observed at top two doses</p>	<p>Parents <u>Male:</u> ↑ size of liver and kidney <u>Female:</u> □ newborn pup size Adult Offspring <u>Male:</u> □ overall growth; ↑ size of liver, kidney, seminal vesicle; □ size of spleen <u>Female:</u> occasional □ overall growth; □ eating</p>
<p>3 mg/kg/d* Parents blood: Female: not measured, estimated to be 120 ppb Male: not measured, not estimated because serum dose response not observed at top two doses</p>	<p>Parents <u>Male:</u> □ overall growth; ↑ eating, ↑ size of liver, kidney, seminal vesicle, and brain; □ size of pituitary <u>Female:</u> □ size of liver; □ breastfeeding; ↑ number of pups (F1 generation) found dead or cannibalized Adult Offspring <u>Male:</u> □ overall growth; ↑ size of liver, kidney, seminal vesicle and testis; □ size of spleen; discolored liver; cellular changes in the liver <u>Female:</u> □ pituitary size; ↑ number of pups (F2 generation) found dead or cannibalized</p>
<p>10 mg/kg/d Parents blood: Female: 370 ppb Male: 51,100 ppb or 51.1 ppm</p>	<p>Parents <u>Male:</u> □ overall growth; ↑ eating; □ size of seminal vesicle; ↑ size of liver, kidney, brain, epididymis, testis, seminal vesicle; cellular changes in the adrenal gland <u>Female:</u> □ size of liver Adult Offspring <u>Male:</u> □ overall growth; ↑ eating: discolored liver; cellular changes in the liver ↑ size of seminal vesicle, testis, epididymis, brain, liver and kidney; □ size of spleen and thymus; <u>Female:</u> occasional □ overall growth; □ pituitary size; ↑ number of pups (F2 generation) found dead or cannibalized</p>
<p>30 mg/kg/d Female: 1020 ppb or 1 ppm Male: 45,300 ppb or 45.3 ppm</p>	<p>Parents <u>Male:</u> □ overall growth, ↑ eating; dehydration; altered size of epididymis, seminal vesicles, prostate, pituitary, adrenal spleen, thymus and kidney; ↑ size of testis, liver, and brain; unkept coat <u>Female:</u> occasional decreases in weight gain and eating, □ size of kidney size; □ breast-feeding; ↑ number of pups (F1 generation) found dead or cannibalized; □ newborn pup size Adult Offspring <u>Male:</u> death, □ overall growth, altered eating, discolored liver, delayed puberty; altered brain and kidney weight; ↑ size of seminal vesicle, testis, epididymis and liver; □ size of spleen, thymus, prostate, and adrenal, cellular changes in adrenal gland and liver <u>Female:</u> death, □ overall growth, □ eating; ↑ number of fertility cycles; delayed puberty; □ pituitary size</p>

Effects found in critical PFOA laboratory studies (page 2 of 2)

6-month monkey study**²	
0 mg/kg/d 20.6 ppb blood	
3 mg/kg/d 98 ppm blood	Death; ↑ liver weight; ↑ total bilirubin
10 mg/kg/d 172 ppm blood	Weight loss; ↑ triglyceride; ↑ liver weight; □ thyroid hormones
30/20 mg/kg/d*** 1084 ppm blood	Death; weight loss; decreased activity; ↑ liver weight; liver lesions; □ thyroid hormones; ↑ triglycerides; altered clinical chemistry; □ liver DNA and ↑ subcellular liver enzymes
Rat cancer study³	
0 mg/kg/d	
1.3 (male); 1.6 (female) mg/kg/d*	Cellular changes in the ovary, lung, and salivary gland; muscle incoordination; possible thyroid tumor
14.2 (male); 16.1 (female) mg/kg/d*	Testicular tumors, mammary gland tumor; cellular effects in the testes, ovary, liver, lung, salivary gland, and possibly, in the thyroid; weight loss; decreased red blood cell measures; increased liver and kidney weight
Rat cancer study (male only, limited organ collection)⁴	
0	
300 ppm ; ~ 14.2 (male); 16.1 (female) mg/kg/d*	Liver, testicular and pancreatic tumors; cellular effects in the testes, pancreas; increased blood estrogen (estradiol); increased liver weight and □-oxidation activity; weight loss

* Serum PFOA not measured

** Serum levels at 4 weeks, when liver enzyme level changes first noted

*** 30 mg/kg/d dose dropped to 20 mg/kg/d when monkeys became noticeably sick; only 2 monkeys in this group dosed the entire time

References:

- 1 York, RG (2002). Oral (gavage) two-generation (one litter per generation) reproduction study of ammonium perfluorooctanoate (APFO) in rats. Report prepared for 3M, St. Paul, MN by Argus Research (Horsham, PA). Sponsor's Study No. T-6889.6., Reviewed in US EPA AR226-1092.
- 2 Butenhoff, J., Costa, G., Elcombe, C., Farrar, D., Hansen, K., Iwai, H., Jung, R., Kennedy, G, Jr., Lieder, P., Olsen, G and Thomford, P. 2002. Toxicity of Ammonium Perfluorooctanoate in Male Cynomolgus Monkeys after Oral Dosing for 6 Months. Toxicol Sci 69(1): 244-257. Also reviewed in US EPA Reviewed in US EPA "Revised Draft PFOA Hazard Assessment-Robust Study Annex" AR226-1137, p. 244-253.
- 3 Sibinski, LJ. 1987. Two-Year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 (perfluorooctane ammonium carboxylate) in rats. Report prepared for 3M, St. Paul, Minnesota by Riker Laboratories Inc. Study No. 0281CR0012; 8EHQ-1087-0394, October 16, 1987 Reviewed in US EPA "Revised Draft PFOA Hazard Assessment-Robust Study Annex" AR226-1137, p. 260-267.
- 4 Biegel, LB., Hurtt, ME., Frame, SR., O'Connor, JC and Cook, JC. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol Sci 60(1): 44-55.



Detailed description of effects found in critical PFOA laboratory animal studies

Rat reproduction study ¹	
0 mg/kg/d Female: < 5.3 ppb blood Male: 34.4 ppb	
1 mg/kg/d* Female: not measured, estimated to be 40 ppb Male: not measured, not estimated because serum dose response not observed at top two doses	<p>Parents <u>Male:</u> ↑ size of liver and kidney (absolute); ↑ size of liver and kidney (relative to body weight) <u>Female:</u> □ newborn pup size (on a litter basis)</p> <p>Offspring <u>Male:</u> □ overall growth (body weight gain, body weight); ↑ size of liver and kidney (absolute); ↑ size of seminal vesicle and kidney (relative to body weight); □ size of spleen (absolute) <u>Female:</u> occasional decreases in overall growth (body weight gain, body weight); □ feeding (absolute)</p>
3 mg/kg/d* Parents blood: Female: not measured, estimated to be 120 ppb Male: not measured, not estimated because serum dose response not observed at top two doses	<p>Parents <u>Male:</u> decreased overall growth (body weight gain, body weight); increased eating relative to body size; ↑ size of liver and kidney (absolute); □ size of pituitary (absolute); ↑ size of seminal vesicle, liver, kidney and brain (relative to body weight) <u>Female:</u> □ size of liver (relative to body weight); □ lactation index and ↑ number of F1 pups found dead or cannibalized</p> <p>Adult Offspring <u>Male:</u> □ overall growth (body weight gain, body weight); discolored liver; ↑ size of liver and kidney (absolute); ↑ size of seminal vesicle, testis, and kidney (relative to body weight); □ size of spleen (absolute); cellular changes in the liver, such as hepatocyte hypertrophy <u>Female:</u> □ pituitary size (absolute and relative to body weight); ↑ number of F2 pups found dead or cannibalized</p>
10 mg/kg/d Parents blood: Female: 370 ppb Male: 51,100 ppb or 51.1 ppm	<p>Parents <u>Male:</u> decreased overall growth (body weight gain, body weight); increased eating relative to body size; □ size of seminal vesicle (absolute); ↑ size of liver and kidney (absolute); ↑ size of epididymis, testis, seminal vesicle, liver, kidney and brain (relative to body weight); cellular changes in the adrenal gland (cortex hypertrophy, vacuolation of the zona glomerulosa) <u>Female:</u> □ size of liver (relative to body weight)</p> <p>Adult Offspring <u>Male:</u> □ overall growth (body weight gain, body weight); ↑ eating relative to body size; discolored liver; cellular changes in the liver, such as hepatocyte hypertrophy; ↑ size of liver (absolute); ↑ size of seminal vesicle, testis, epididymis, brain and kidney (relative to body weight); □ size of spleen and thymus (absolute) <u>Female:</u> occasional decreases in overall growth (body weight gain); □ pituitary size (absolute and relative to body weight); ↑ number of F2 pups found dead or cannibalized</p>
30 mg/kg/d Female: 1020 ppb or 1 ppm Male: 45,300 ppb or 45.3 ppm	<p>Parents <u>Male:</u> decreased overall growth (body weight gain, body weight); increased eating relative to body size; dehydration; unkept coat; □ size of epididymis, seminal vesicles, prostate, pituitary, adrenal spleen, thymus and kidney (absolute size); ↑ size of epididymis, testis, seminal vesicle, liver, kidney, adrenal and brain (relative to body weight) <u>Female:</u> occasional decreases in weight gain and eating; □ size of kidney size (absolute and relative to body weight); □ lactation index and ↑ number of F1 pups found dead or cannibalized; □ newborn pup size (on a litter basis)</p> <p>Adult Offspring <u>Male:</u> death; □ overall growth (body weight gain, body weight); altered eating relative to body size; delayed sexual maturation [preputial separation (significant after accounting for weight, but not after accounting for gestation age – although gestational length did not differ in parental animals)]; ↑ size of liver (absolute); ↑ size of seminal vesicle, testis, epididymis, brain and kidney (relative to body weight); □ size of spleen, thymus, kidney, prostate, brain, and adrenal (absolute); discolored liver; cellular changes in adrenal (cortex hypertrophy, vacuolation of zona glomerulosa) and liver, such as hepatocyte hypertrophy <u>Female:</u> death; □ overall growth (body weight gain, body weight); □ feeding (absolute); ↑ number of fertility cycles (estrous cycles per 21 days); delayed puberty [vaginal opening (significant after accounting for weight, but not after accounting for gestation age – although gestational length did not differ in parental animals)]; □ pituitary size (absolute and relative to body weight)</p>

Detailed description of effects found in critical PFOA laboratory animal studies - continued

6-month monkey study**²	
0 mg/kg/d 20.6 ppb blood	
3 mg/kg/d 98 ppm blood	Death (animal had hind-limb paralysis, muscle incoordination, no response to touch); ↑ liver weight; ↑ total bilirubin
10 mg/kg/d 172 ppm blood	Weight loss; ↑ triglyceride; ↑ liver weight; □ thyroid hormones
30/20 mg/kg/d*** 1084 ppm blood	Death; weight loss; decreased activity; ↑ liver weight; liver lesions; □ thyroid hormones; ↑ triglycerides; altered clinical chemistry (↑ triglyceride, ↑ serum enzymes, ↑ bile acid concentration, □ neutrophil count, □ total protein, □ albumin); □ liver DNA; ↑ subcellular liver marker enzymes [succinate dehydrogenase (SDH), peroxisomal marker – CN ⁻ insensitive palmitoyl CoA oxidation (PCO)]
Rat cancer study³	
0 mg/kg/d	
1.3 (male); 1.6 (female) mg/kg/d*	Cellular changes in the ovary (tubular hyperplasia) lung [vascular mineralization (female only)], and salivary gland [lesions (male only)]; muscle incoordination (female only); possible thyroid tumor (C-cell adenoma; male only)
14.2 (male); 16.1 (female) mg/kg/d*	Testicular tumors (Leydig cell adenoma), mammary gland tumors (fibroadenoma); cellular effects in the testes (vascular mineralization), ovary (tubular hyperplasia), liver [cystoid degeneration (male only), megalocytosis, portal mononuclear cell infiltration (male only)], lung [alveolar macrophages (male only), hemorrhage (male only)], salivary gland [lesions (male only)], and possibly thyroid (C-cell hyperplasia, female only); weight loss; decreased red blood cell measures (male only); increased liver weight (male only) and kidney weight
Rat cancer study (male only, limited organ collection)⁴	
0	
300 ppm ; ~ 14.2 (male); 16.1 (female) mg/kg/d*	Liver tumors (adenomas); testicular tumors (Leydig cell adenoma); pancreatic tumors (acinar cell adenoma/carcinoma); cellular effects in the testes (hyperplasia), pancreas (hyperplasia, cell proliferation); increased blood estrogen (estradiol); increased liver weight and □-oxidation activity; weight loss

* Serum PFOA not measured

** Serum levels at 4 weeks, when liver enzyme level changes first noted

*** 30 mg/kg/d dose dropped to 20 mg/kg/d when monkeys became noticeably sick; only 2 monkeys in this group dosed the entire time

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- 4 Biegel, LB., Hurtt, ME., Frame, SR., O'Connor, JC and Cook, JC. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol Sci 60(1): 44-55.