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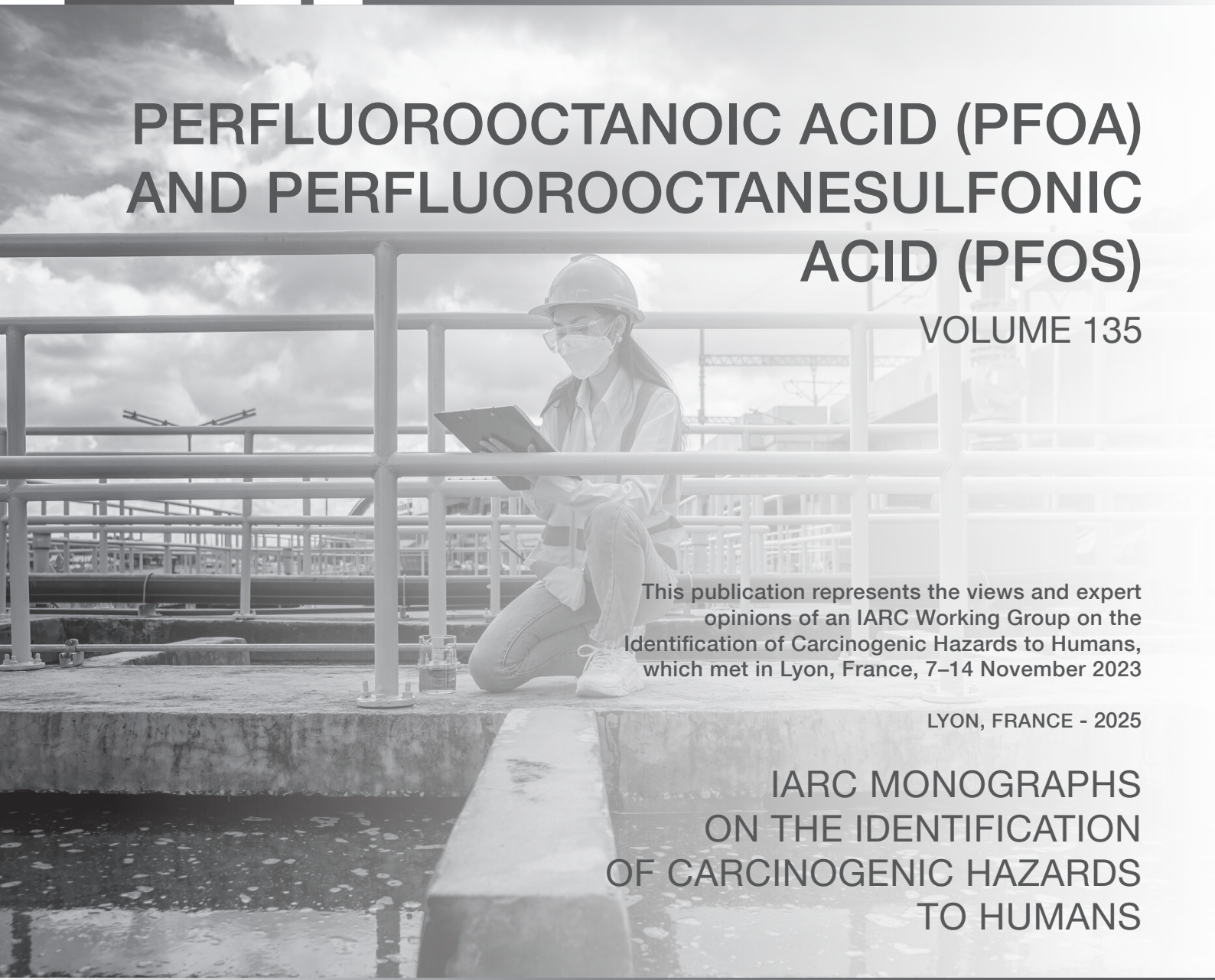

# PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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International Agency for Research on Cancer

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**Table S4.25 End-points relevant to modulation of receptor-mediated effects in experimental systems in vivo exposed to PFOA or PFOS**

| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| ***Peroxisome proliferator-activated receptor α (PPARα)*** | | | |
| Cynomolgus monkey (M) | PFOA, 0, 3, 10, 20/30 mg/kg/day, 26 weeks, oral | ↑ Hepatic palmitoyl coA oxidase (PCO) activity (in 20/30mg/kg/day group only). | Butenhoff et al. (2002) |
| Crl:CD rat (M) | PFOA (linear, branched, and mixed linear/branched isomers of APFO), 0, 0.3, 1, 3, 10, or 30 mg/kg/day, 14 days, oral | ↑ Liver weight: branched ≥ 1 mg/kg; linear or linear/branched ≥ 3 mg/kg,<br>↑ PCO activity: branched ≥ 3 mg/kg; linear or linear/branched ≥ 1 mg/kg | Loveless et al. (2006) |
| Crl:CD rat (M) | PFOA (as APFO), 0, 1, 10, 30 or 100 mg/kg/day (equivalent to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg/day), up to 90 days, oral [diet] | ↑ Liver weight: ≥ 10 ppm;<br>↑ PCO activity: ≥ 10 ppm;<br>↑ minimal to mild hepatocyte hypertrophy ≥ 10 ppm.<br>Effects were reversible after an 8-week recovery. | Perkins et al. (2004) |
| CD1 mice (PF) | PFOA, 0 or 5 mg/kg/day, GD 1–17, oral | Liver PPARα mRNA: ↓ on PND 1, 14, ↑ on PND21,<br>PPARα protein: ↓ on PND14, ↑ on PND28,<br>Effects on PPAR expression were also seen in heart, kidney, and other organs. | Abbott et al. (2012) |
| Sv/129 mice (PF)<br>PPARα$^{-/-}$ mice (PF)<br>hPPARα mice (PF) | PFOA, 0 or 3 mg/kg/day, GD 1–17, oral | Maternal liver (GD 18):<br>↑ *Acox1* and *Cyp4a10* mRNA in WT,<br>↑ *Cyp4a10* mRNA in hPPARα;<br>↑ *Cyp2b10* and *Cyp3a11* mRNA in WT, PPARα-null, and hPPARα. | Albrecht et al. (2013) |
| C57BL/6 mice (M) | PFOA, 0 or 40 mg/kg, IP | No effect on PPARα mRNA.<br>↑ Cyp2B10 and 4A14 at both mRNA and protein levels. | Cheng and Klaassen (2008) |
| Kunning mice (PF) | PFOA, 0, 1, 2.5, 5, or 10 mg/kg/day, GD1–17, oral | ↓ Liver PPARα mRNA at 2.5 and 5 mg/kg/day. | Li et al. (2019a) |

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| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| C57BL/6 mice (M) | PFOA, 0 or 1 mg/kg/day, up to 16 weeks, oral | ↑ Liver PPARα mRNA at 8 weeks only. | Li et al. (2019c) |
| CD-1 mice (M) | PFOA (linear, branched, and mixed linear/branched isomers), 0, 0.3, 1, 3, 10, or 30 mg/kg/day, 14 days, oral | ↑ Liver weight, ↑ PCO activity. | Loveless et al. (2006) |
| Sv/129 mice<br>mPPARα mice (M)<br>PPARα$^{-/-}$ mice (M)<br>hPPARα mice (M) | PFOA, 0, 1, or 5 mg/kg/day for 6 weeks, oral | ↑ Liver PPARα mRNA in mPPARα in controls at 1 mg/kg<br>↑ CYP4A10 and PH mRNA in mPPARα and hPPARα mice, but not in PPARα -/- mice. | Nakagawa et al. (2012) |
| 129S1/SvImJ mice (M)<br>PPARα$^{-/-}$ mice (M) | PFOA, 0, 1, or 3 mg/kg/day, 7 days, oral | ↑ Aox1<br>↑ Slc27a1 in liver from wild-type mice only. | Rosen et al. (2008a) |
| PPARα$^{-/-}$ mice (F, M)<br>hPPARα mice (F, M) | PFOA, 0 or 8 μM, 6–7 weeks, oral (dw) | No difference Liver PPARα mRNA in hPPARα mice.<br>↑ Liver Acox1 mRNA in hPPARα mice. | Schlezinger et al. (2020) |
| BALB/c mice (M) | PFOA, 0, 0.08, 0.31, 1.25, 5, or 20 mg/kg/day, 28 days, oral | ↑ Liver PPARα expression at 0.08 and 0.31 mg/kg/day. | Yan et al. (2015b) |
| PPARα$^{-/-}$ mice (M)<br>SV/129 (M) | PFOA, 0, 1, 3, or 10 mg/kg/day, 7 days, oral | ↑ Liver weight (both strains),<br>↑ hepatic cell proliferation (both strains, 10mg dose only),<br>↑ hepatocyte hypertrophy (both strains). | Wolf et al. (2008b) |

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| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| PPARα$^{-/-}$ mice (M)<br>C57Bl/6 (M) | PFOA, 0 or 0.02%, 7 days, oral (diet), | ↑ Liver weight (both strains),<br>↑ hepatic PCO activity (wildtype only). | Yang et al. (2002a) |
| C57BL/6 (M)<br>PPARα$^{-/-}$ mice (M) | PFOA, 0, 1, or 3 mg/kg/day, 7 days, oral | WT Liver:<br>↑ Cyp4a14 and Cyp2b10 mRNA. No change PPARα mRNA.<br>PPARα$^{-/-}$ liver:<br>↑ Cyp4a14, Cyp3a11, and Cyp2b10 mRNA. | Wen et al. (2019) |
| C57BL/6 mice (M) | PFOA, 0 or 40 mg/kg, IP | No effect on PPARα mRNA.<br>↑ Cyp2B10 and 4A14 at both mRNA and protein levels. | Cheng and Klaassen (2008) |
| E3L.CETP mice (M) | PFOS, 0 or 3 mg/kg/day, 4–6 wk, oral | Hepatic gene expression profiling data resulted from mixed PPARα and PXR activation.<br>Activation of lipid metabolism pathways. | Bijland et al. (2011) |
| C57BL/6 (M)<br>129/Sv mice (PPARα$^{-/-}$)(M)<br>129/Sv mice (WT) | PFOS, 0, 0.001 (WT only), 0.005, or 0.02%, 10 days, oral | ↑ Liver weight (in all three strains strains). | Qazi et al. (2009) |
| 129S1/SvImJ mice (M)<br>PPARα$^{-/-}$ mice (M) | PFOS, 0, 3, or 10 mg/kg/day, 7 days, oral | Liver microarray data suggest activation of PPARα pathway in wild type mice. Gene pathways associated with ribosome biogenesis, oxidative phosphorylation, and cholesterol biosynthesis were activated in null mice. | Rosen et al. (2010) |
| Sv/129 mice (M) | PFOS, 0, 0.003 for 28 days, or 0.006% for 7 days, diet | ↑ Liver Acox1 and Cyp4a10 mRNA in Sv/129 mice at 0.003% for 28 days. | Su et al. (2022b) |

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| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| PPARα$^{-/-}$ mice (M)<br>hPPARα mice (M) | | ↑ Liver Cyp2b10 and Cyp3a11 mRNA in all mice at 0.003% for 28 days. Hepatomegaly caused by PFOS does not require mouse or human PPARα and could be due to effects induced by activation of CAR and/or PXR. | |
| BALB/c mice (M) | PFOS, 0, 5, or 20 mg/kg/day, 14 days, oral | No effect on liver PPARα expression in mice on regular diet,<br>↓ liver PPARα expression in mice on high fat diet at 20 mg/kg/day. | Wang et al. (2014b) |
| ICR mice (M) | PFOS, 0, 0.2, or 1 mg/kg/day, 10 days, oral | ↑ Liver fibroblast growth factor 21 (FGF21) mRNA at ≥ 0.2 mg/kg.<br>↑ Liver and serum FGF21 concentration at 1 mg/kg. | Wang et al. (2014b) |
| Sprague-Dawley rat (F, M) | PFOS, 0, 2, 20, 50, or 100 ppm<br>(male rats: 0, 0.14, 1.33, 3.21, or 6.34 mg/kg/d;<br>female rats: 0, 0.15, 1.43, 3.73, or 7.58 mg/kg/d), 28 days, diet | ↑ liver *ACOX1* expression at ≥ 50 ppm (F, M)<br>↑ liver *CYP4A22* expression at ≥ 20 ppm (M) and ≥ 50 ppm (F). | Curran et al. (2008) |
| Sprague-Dawley rat (M) | PFOS, 0 or 50 ppm, 28 days, diet | Altered liver expression of 48 genes in the PPARα pathway as well as transcripts that may mediate PFOS-induced effects on TH homeostasis including: activation of the CAR/PXRpathway, phase II/III enzymes, and deiodinase. | Dong et al. (2016) |
| Sprague-Dawley rat (M) | PFOS, 0, 20, or 100 ppm, 7 days, diet | ↑ Liver Acox1protein levels at ≥ 20 ppm. | Elcombe et al. (2012a) |
| Sprague-Dawley rat (F, M) | PFOS, 0, 0.5, 2.0, 5.0, or 20 ppm, 4 or 14 weeks, diet | ↑ Relative liver weight at 20 ppm (both sexes) at 14 week,<br>PCO activity: no change at 14 week. | Seacat et al. (2003) |
| Sprague-Dawley rat (M) | PFOS, 0, 20, or 100 ppm, up to 28 days, diet | ↑ Liver PPARα target gene (e.g. Acox1)protein levels at 100 ppm.<br>↑ Relative liver weight, hepatocellular hypertrophy<br>↑ hepatic PCO activity (1.4-fold). | Elcombe et al. (2012b) |
| ***Peroxisome proliferator-activated receptor β/delta (PPARβ/δ)*** | | | |

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|---|---|---|---|
| C57BL/6 mice (M) | PFOA, 0 or 1 mg/kg/day, up to 16 weeks, oral | ↓ Liver PPARδ mRNA at 8 and 16 weeks. | Li et al. (2019b) |
| BALB/c mice (M) | PFOA, 0, 0.08, 0.31, 1.25, 5, or 20 mg/kg/day, 28 days, oral | No effect on liver PPARβ/δ expression. | Yan et al. (2015b) |
| ***Peroxisome proliferator-activated receptor gamma (PPARγ)*** | | | |
| CD1 mice (PF) | PFOA, 0 or 5 mg/kg/day, GD 1–17, oral | ↓ Liver PPARγ mRNA PND1;<br>↑ Liver PPARγ mRNA on GDs 21, 28.<br>Effects on PPAR expression were also seen in heart, kidney, and other organs. | Abbott et al. (2012) |
| Sv/129 mPPARα mice (M)<br>PPARα$^{-/-}$ mice (M)<br>hPPARα mice (M) | PFOA, 0,1.0, or 5.0 mg/kg/day for 6 weeks, oral | ↑ Liver PPARγ mRNA all strains. | Nakagawa et al. (2012) |
| PPARα$^{-/-}$ mice (F, M)<br>hPPARα mice (F, M) | PFOA, 0 or 8 μM, 6–7 weeks, oral (dw) | ↑ Liver expression of PPARγ mRNA (Nr1c3) and PPARγ target gene (Cd36) in both sexes and strains.<br>↑ Liver expression of PPARγ target gene (Fabp4) in both sexes of hPPARα mice. | Schlezinger et al. (2020) |
| BALB/c mice (M) | PFOA, 0, 0.08, 0.31, 1.25, 5, or 20 mg/kg/day, 28 days, oral | ↑ Liver PPARγ mRNA at ≥ 0.31 mg/kg. | Yan et al. (2015b) |
| C57BL/6 mice (PF) | PFOS, 0 or 0.3 mg/kg/day, throughout pregnancy, oral | ↑ Brain PPARγ mRNA. | Wan Ibrahim et al. (2013) |

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| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| ***Constitutive androstane receptor/ pregnane X receptor (CAR/PXR)*** | | | |
| C57BL/6 mice (NS) | PFOA, 0 or 20 mg/kg/day, 3 days IP | ↑ *Cyp2b10* mRNA levels in WT only. | Abe et al. (2017) |
| *Car*-null mice (NS) | | | |
| C57BL/6 mice (M) | PFOA, 0 or 40 mg/kg, IP | ↑ Nuclear liver CAR mRNA and protein. | Cheng and Klaassen (2008) |
| C57BL/6 mice (M) | PFOA, 0 or 1 mg/kg/day, up to 16 weeks, oral | ↑ Liver CAR and PXR mRNA at ≥ 2 weeks. | Li et al. (2019b) |
| PPARα$^{-/-}$ mice (F, M) | PFOA, 0 or 8 μM, 6–7 weeks, oral (dw) | ↑ Liver CAR mRNA (Nr1i3) in male hPPARα mice only. | Schlezinger et al. (2020) |
| hPPARα mice (F, M) | | ↑ Liver expression CAR target genes (Cyp2b10, Gstm3) in both sexes and both genotypes. | |
| | | CAR target gene expression in PPARα$^{-/-}$ mice > hPPARα mice. | |
| E3L.CETP mice (M) | PFOS, 0 or 3 mg/kg/day, 4–6 wk, oral | Hepatic gene expression profiling data resulted from combined PPARα and PXR activation. | Bijland et al. (2011) |
| CD-1 mice (PF) | PFOS, 0, 0.3, 3 mg/kg/day, throughout pregnancy, oral | Male offspring testes LXR/RXR and PXR/RXR activation on PND1. | Lai et al. (2017a) |
| Sprague-Dawley rat (M) | PFOS, 0 or 50 ppm, 28 days, diet | Altered liver expression of 29 genes in CAR/PXR pathway. | Dong et al. (2016) |
| Sprague-Dawley rat (M) | PFOS, 0, 20, or 100 ppm, 7 days, diet | ↑ Liver expression of CAR target gene (pentoxyresorufin-O-depentylase activity) at 100 ppm. | Elcombe et al. (2012a) |
| | | ↑ Liver expression of PXR target gene (testosterone 6 β-hydroxylase) at ≥ 20 ppm. | |

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| Experimental system | Exposure | Relevant finding | Reference |
|---|---|---|---|
| Sprague-Dawley rat (M) | PFOS, 0, 20, or 100 ppm, up to 28 days, diet | ↑ Liver expression of CAR target gene (pentoxyresorufin-O-depentylase activity) at 100 ppm.<br>↑ Liver expression of PXR target gene (testosterone 6 β-hydroxylase) at 100 ppm (> day 7) and 20 ppm (day 28). | Elcombe et al. (2012b) |
| ***Estrogen receptor (ER)*** | | | |
| C57BL/6 mice (M) | PFOS, 0 or 5.0 mg/kg/day, 28 days, oral | ↑ Hepatic ERβ protein;<br>No effect on hepatic ERα protein. | Xu et al. (2017) |
| CD-1 mice (F) | PFOA 0, 0.005, 0.01, 0.02, 0.05, 0.1, or 1 mg/kg/day, PND 18–20, oral | No changes in relative expression of mRNA encoding ER target genes in the uterus including TFF1, TFF2, TFF3. | Yao et al. (2014) |
| ***Androgen receptor (AR)*** | | | |
| C57BL/6 (M)<br>129/Sv (wt)(M)<br>129/Sv (PPARα$^{-/-}$)(M) | PFOS, 0, 0.001 (WT only), 0.005, or 0.02%, 7 days, oral | ↓ Epididymis weight (C57BL/6 and 129/Sv (wt) only at 0.02%). | Qazi et al. (2009) |
| Sprague-Dawley rat (M) | PFOS, 0, 1.0, 3.0, or 6.0 mg/kg/day, 28 days, oral | ↓ Testis AR mRNA and protein at ≥ 1 mg/kg/day | López-Doval et al. (2016) |
| ***Follicle-stimulating hormone receptor (FSHR)*** | | | |
| Sprague-Dawley rat (M) | PFOS, 0, 1.0, 3.0, or 6.0 mg/kg/day, 28 days, oral | ↓ Testis FSHR mRNA and protein at ≥ 1 mg/kg/day | López-Doval et al. (2016) |
| ***Luteinizing hormone receptor (LHR)*** | | | |

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|---|---|---|---|
| Sprague-Dawley rat (M) | PFOS, 0, 1.0, 3.0, or 6.0 mg/kg/day, 28 days, oral | ↓ Testis LHR protein at ≥ 1 mg/kg/day, ↑ LHR mRNA at ≥ 1 mg/kg/day | López-Doval et al. (2016) |
| ***Other receptors*** | | | |
| ICR mice (M) | PFOA, 0, 0.2, or 1 mg/kg/day, 10 days, oral | ↑ Brain corticotropin-releasing hormone receptor 1 (CRF-1) mRNA at 1 mg/kg. | Wang et al. (2014b) |
| BALB/c mice (M) | PFOA, 0, 0.08, 0.31, 1.25, 5, or 20 mg/kg/day, 28 days, oral | ↓ Liver HnF4α expression at 1.25 and 5 mg/kg/day. | Yan et al. (2015b) |
| CD-1 mice (F) | PFOA 0, 0.005, 0.01, 0.02, 0.05, 0.1, or 1 mg/kg/day, PND 18–20, oral | No changes in relative expression of mRNA encoding the progesterone receptor | Yao et al. (2014) |

AFPO, ammonium perfluorooctanoate; AR, androgen receptor; bw, body weight; CAR, constitutive androstane receptor; CRF, corticotropin-releasing hormone receptor; CYP, cytochrome P450; F, female; GD, gestational day; ER, estrogen receptor; FGF, fibroblast growth factor; FSHR, follicle-stimulating hormone receptor; GSTM3, glutathione *S*-transferase of the mu class; IP, intraperitoneal; LHR, luteinizing hormone receptor; LXR, liver X receptor; M, male; Nrf2, nuclear factor erythroid 2–related factor 2; NS, not specified; Oatp, organic anion transporting polypeptides; PCO, palmitoyl CoA oxidase; PF, pregnant female; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PND, postnatal day; PPAR, peroxisome proliferator-activated receptor; ppm, parts per million; wk, week; PXR, pregnane X receptor; RXR, retinoid X receptor; TH, thyroid hormone; TFF, trefoil factor; WT, wildtype.