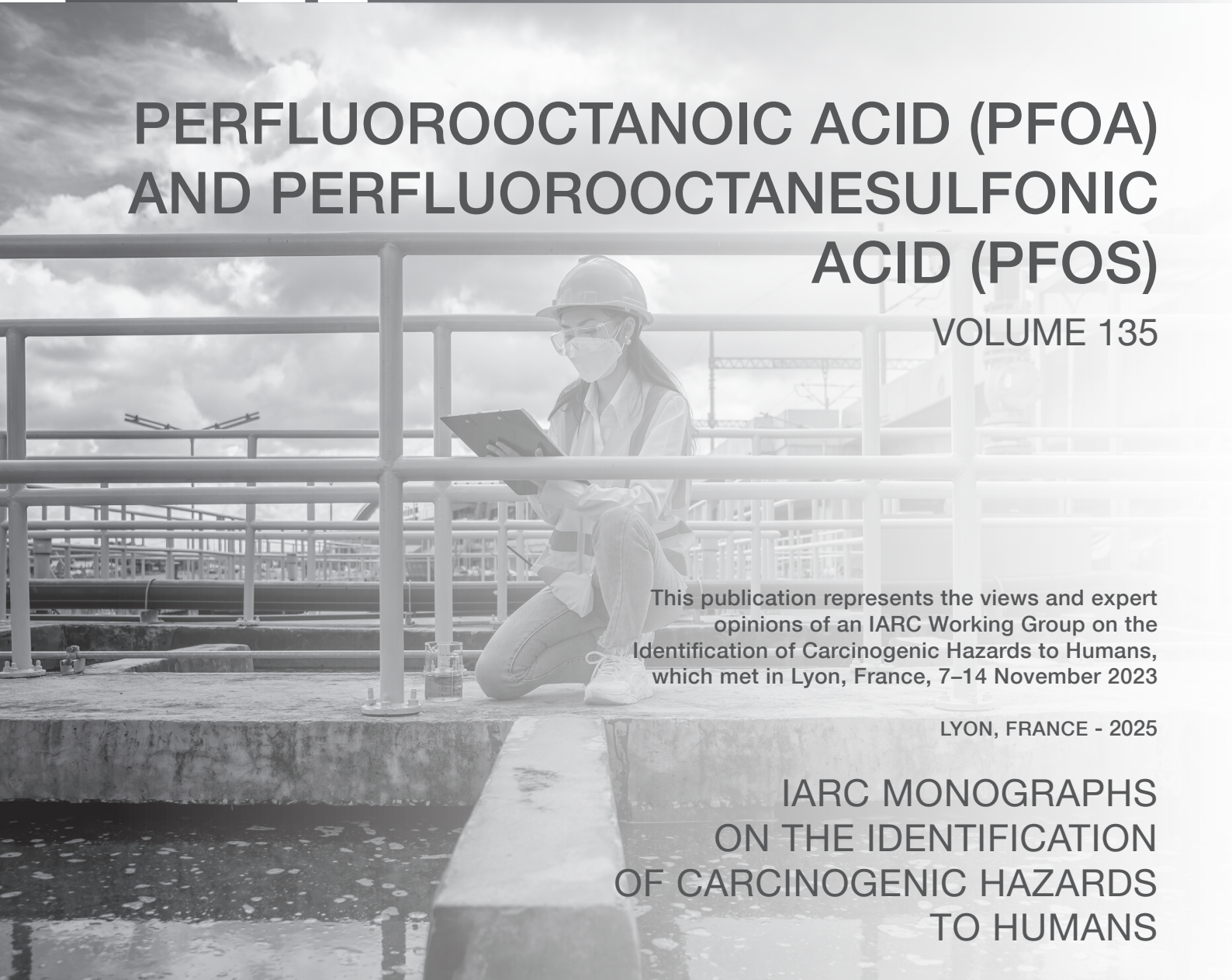


# PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

VOLUME 135



This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 November 2023

LYON, FRANCE - 2025

IARC MONOGRAPHS  
ON THE IDENTIFICATION  
OF CARCINOGENIC HAZARDS  
TO HUMANS

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
<i>Thyroid hormone effects</i>			
Cynomolgus monkey (F, M)	PFOS, 0 or 9 mg/kg (once) or 11 to 17.2 mg/kg (three doses total), dosing was spaced 70 to 245 days apart, oral	No statistically significant change in serum TSH, FT4, or TT3. ↓ Serum TT4 concentration was not deemed to be clinically significant.	Chang et al. (2017)
CD-1 mice (PF)	PFOS, 0, 1, 5, 10, 15, or 20 mg/kg/day, GD 1–17, oral	No change in pup serum TT4 concentration.	Lau et al. (2003)
CD-1 mice (PF)	PFOS, 0, 1.5, 3, or 6 mg/kg/day, GD 6–18, oral	No change in maternal serum TT4, TT3, FT3, or FT4 concentrations.	Fuentes et al. (2006)
ICR mice (F)	PFOS, 0 or 10 mg/kg/day, 14 days, oral	↓ Serum T3 and T4 concentrations.	Wang et al. (2018b)
Sprague-Dawley rat (F)	PFOS, 0 or 5 mg/kg/day, 3 days, oral	↓ Serum FT4 and TT4 concentrations. No statistically significant change in serum TSH concentration.	Chang et al. (2007)
Sprague-Dawley rat (F)	PFOS, 0 or 15 mg/kg, oral	↓ Serum TT4, TT3, rT3 concentrations. No statistically significant change in serum TSH concentration 24 h past treatment.	Chang et al. (2008)
Sprague-Dawley rat (PF)	PFOS, 0, 0.1, 0.3, or 1 mg/kg/day, GD 0 to PND 20, oral	No statistically significant change in dam or pup serum TSH concentration.	Chang et al. (2009)
Sprague-Dawley rat (PF)	PFOS, 0, 0.1, 0.3, 1, 3, 10, or 30 mg/kg/day, GD 14 to GD 18, oral	↓ Maternal serum TT3 and TT4 concentrations at ≥ 10 mg/kg/day.	Conley et al. (2022)
Sprague-Dawley rat (M)	PFOS, 0 or 3 mg/kg/day, 7 days, oral	↓ Serum TT4, TT3, and rT3 concentrations. No statistically significant change in serum TSH concentration.	Davidson et al. (2022)
Sprague-Dawley rat (F, M)	PFOS, 0, 2, 20, 50, or 100 ppm (equivalent to 0, 0.14, 1.33, 3.21, or 6.34 mg/kg/d in males and 0, 0.15, 1.43, 3.73, 7.58 mg/kg/d in females), 28 days, diet	↑ Relative thyroid/body weight at 100 ppm; ↓ T3 concentration at 100 ppm (M); ↓ T3 concentration at ≥ 50 ppm (F); ↓ T4 concentration at ≥ 20 ppm (F and M).	Curran et al. (2008)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
Sprague-Dawley rat (M)	PFOS, 0 or 50 ppm, 28 days, diet	Altered expression of genes involved in TH conversion, metabolism, and clearance.	Dong et al. (2016)
Sprague-Dawley rat (PF)	PFOS, 0, 1, 2, 3, or 5 mg/kg/day, GD 2–21, oral	↓ Pup TT4 concentration at PND 2; ↓ pup FT4 concentration at PND 2–35 (in all dosage groups). No change in pup T3, TSH, or TT4 concentration at PND 21.	Lau et al. (2003)
Wistar rat (PF)	PFOS, 0 or 3.2, 32 ppm, GD 1-PND 14, diet	↓ Maternal TT4 concentration at PND1, neonatal TT4 concentration at PND7 and maternal and neonatal TT4 concentration at PND 14. No effect on TT3 concentration.	Wang et al. (2011b)
Sprague-Dawley rat (M)	PFOS, 0, 1.7, 5.0, or 15.0 mg/L, 91 days, oral (dw)	No effect on relative thyroid weight, ↑ serum TT3 concentration at 1.7 mg/L only, ↓ serum TT4 concentration at ≥ 1.7mg/L, ↓ serum FT4 concentration at 5 mg/L only, no effect on serum TSH concentration or TSH receptor mRNA.	Yu et al. (2009a)
Wistar rat (M, F)	PFOS, 0, 3.2 ppm, GD 1 – PND 21, diet	↓ Pup serum TT4 concentration at PND 21 and 35. No effect on pup serum TT3 concentration.	Yu et al. (2009b)
Wistar rat (F)	PFOS, 0, 0.2, 1.0, or 3.0 mg/kg/day, 5 days, oral	No effect on relative thyroid weight at 3 mg/kg/day. ↓ Serum TT4 concentration at ≥ 1 mg/kg/day, ↓ serum TT3 concentration at 3 mg/kg/day. No effect on biliary TT4 or TT3 concentrations.	Yu et al. (2011)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
Cynomolgus monkey (M)	Ammonium perfluorooctanoate (APFO), 0, 3, 10, 20/30 mg/kg/day, 26 weeks, oral	↑ Serum FT3 and TT3 concentrations. No changes in serum TSH, FT4, TT4 concentrations.	Butenhoff et al. (2002)
CD-1 mouse (PF)	PFOA, 0, 1 or 5 mg/kg/day, 10 or 16 days, oral	No effect on placental T3, T4, or rT3 concentrations.	Blake et al. (2020)
Crl:CD rat (M, F)	PFOA, 0 or 30 mg/kg/day, 28 days, oral	↓ Serum TT4 and FT4 concentrations. ↓ Serum TSH in males. ↓ Serum TSH levels in males and TT4 and FT4 levels in females recovered after 3 wk recovery period. ↑ Liver Thrsp mRNA.	Butenhoff et al. (2012a)
<i>Estrogenic hormone effects</i>			
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 wk, oral	No effect on serum or testicular estradiol concentration.	Huang et al. (2022a)
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 wk, oral	No effect on serum or testicular estradiol concentration.	Qiu et al. (2021)
C57BL/6 mice (M)	PFOS, 0, 0.5, or 10.0 mg/kg/day, 5 weeks, oral	No effect on serum estradiol concentration.	Qu et al. (2016)
BALB/c mice (M)	PFOS, 0, 5, or 20 mg/kg/day, 14 days, oral	No effect on serum estradiol concentration.	Wang et al. (2014b)
ICR mice (F)	PFOS, 0 or 10 mg/kg/day, 14 days, oral	↓ Serum estradiol concentration on day14.	Wang et al. (2018b)
C57BL/6 mice (PF)	PFOS, 0, 0.1, 1.0, or 5.0 mg/kg/day, GD 1–17, oral	↑ Serum estradiol concentration in male pups at 5 mg/kg/day on PND 28. No effect on female pup serum estradiol concentration.	Zhong et al. (2016)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0, 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Serum estradiol concentration at ≥ 1 mg/kg/day.	López-Doval et al. (2015)
Sprague-Dawley rat (F)	PFOS, 0 or 15 mg/kg/day, 28 days, oral	↑ Serum estradiol concentration for both PFOS and PFOA.	Qiu et al. (2020)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
Sprague-Dawley rat (M)	PFOS, 0, 3, or 6 mg/kg/day, 28 days, oral	↓ Serum estradiol concentration at ≥ 3 mg/kg/day	Salgado et al. (2015)
Cynomolgus monkey (M)	Ammonium perfluorooctanoate (APFO), 0, 3, 10, 20/30 mg/kg/day, 26 weeks, oral	No effect on serum estradiol concentration	Butenhoff et al. (2002)
CrI:CD rat (M)	Ammonium perfluorooctanoate (APFO), 0, 1, 10, 30 or 100 ppm (equivalent to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg/day), up to 90 days, oral	No effect on serum estradiol concentration.	Perkins et al. (2004)
Wistar rat (M)	PFOA, 0, 0.015, or 0.15 mg/kg/day, 2 months, oral	↑ Serum estradiol concentration at ≥ 0.015 mg/kg/day.	Han et al. (2022)
CD-1 mice (PF)	PFOA, 0, 0.01, 0.1, 0.3 or 1.0 mg/kg/day, GD 1–17, oral	No effect on female offspring serum estradiol concentration.	Tucker et al. (2015)
C57Bl/6 mice (PF)			
CD-1 mice (F)	PFOA, 0, 1, 5, 10 or 20 mg/kg/day, 10 days, oral	No effect on serum estradiol concentration.	Yang et al. (2022)
ICR mice (F)	PFOA, 0, 0.5, 2, or 5 mg/kg/day, 28 days, oral	↓ Serum estradiol concentration at 5 mg/kg/day	Zhang et al. (2020b)
CrI:CD rat (M)	PFOA, 0 or 300 ppm, 3 to 24 months, diet	↑ Serum estradiol concentration between 1 and 12 months	Biegel et al. (2001)
Sprague-Dawley rat (F)	PFOA, 0 or 15 mg/kg/day, 28 days, oral	↑ Serum estradiol concentration	Qiu et al. (2020)
Sprague-Dawley rat (F)	PFOA, 0 or 0.01 mg/kg/day, 21 days, oral	No effect on serum estradiol concentration	Su et al. (2022a)
C57Bl/6 mice (F)	PFOA, 0 or 5 mg/kg/day, 4 weeks after ovulation at 3 week-age, oral	No effect on serum estradiol concentration.	Zhao et al. (2010)
<b><i>Androgen hormone effects</i></b>			
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 weeks, oral	↓ Serum and testicular testosterone concentration at ≥ 5 mg/kg/day.	Huang et al. (2022a)
CD-1 mice (M)	PFOS, 0, 1, or 5 mg/kg/day, 21 days, oral	No effect on serum testosterone concentrations.	Li et al. (2022e)
C57BL/6 mice (M)	PFOS, 0, 0.5, or 10.0 mg/kg/day, 5 weeks, oral	↓ Serum testosterone concentration at 10 mg/kg/day.	Qu et al. (2016)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 weeks, oral	↓ Serum and testicular testosterone at ≥ 5 mg/kg/day.	Qiu et al. (2021)
CD-1 mice (M)	PFOS, 0, 1, 5, or 10 mg/kg/day, up to 21 days, oral	↓ Epididymal sperm count and serum testosterone at 10 mg/kg/day	Wan et al. (2011)
BALB/c mice (M)	PFOS, 0, 5, or 20 mg/kg/day, 14 days, oral	No effect on serum testosterone concentration	Wang et al. (2014b)
C57BL/6 mice (PF)	PFOS, 0, 0.1, 1.0, or 5.0 mg/kg/day, GD 1–17, oral	↓ Serum testosterone concentration in male pups at 5 mg/kg/day on PND 28 and at 1 mg/kg/day on PND56. No effect on female pup serum testosterone concentration	Zhong et al. (2016)
Wistar rat (M)	PFOS, 0, 0.015, or 0.15 mg/kg/day, 60 days, oral	↑ Serum testosterone concentration at ≥ 0.015 mg/kg/day	Alam et al. (2021)
Wistar (M)	PFOS, 0, 0.015, or 0.15 mg/kg/day, 2 months, oral	↑ Serum testosterone concentration at ≥ 0.015 mg/kg/day.	Han et al. (2022)
Sprague-Dawley rat (M)	PFOS, 0, 5; or 10, mg/kg/day, 21 days, oral	↓ Serum testosterone concentration at ≥ 5 mg/kg/day	Li et al. (2018d)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Serum testosterone concentration at ≥ 0.5 mg/kg/day	López-Doval et al. (2014)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Serum testosterone concentration at ≥ 0.5 mg/kg/day	López-Doval et al. (2015)
Sprague-Dawley rat (M)	PFOS, 0 or 20 mg/kg/day, 56 days, oral	↓ Plasma testosterone concentration.	Umar Ijaz et al. (2022)
Sprague-Dawley rat (PF)	PFOS, 0, 5; or 20, mg/kg/day, GD 11–19, oral	↓ Male offspring testicular testosterone concentration at 20 mg/kg/day.	Zhao et al. (2014)
Cynomolgus monkey (M)	Ammonium perfluorooctanoate (APFO), 0, 3, 10, 20/30 mg/kg/day, 26 weeks, oral	No effect on serum testosterone concentration.	Butenhoff et al. (2002)
mPPAR $\alpha$ mice (M)	Ammonium perfluorooctanoate (APFO), 0, 1, or 5 mg/kg/day for 42 days, oral	↓ Plasma testosterone concentration in mPPAR $\alpha$ mice at 5 mg/kg/day.	Li et al. (2011)
PPAR $\alpha$ <sup>-/-</sup> mice (M)			

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
hPPAR $\alpha$ mice (M)		↓ Plasma testosterone concentration in hPPAR $\alpha$ mice at $\geq 1$ mg/kg/day.  No effect plasma testosterone concentration in PPAR $\alpha^{-/-}$ mice.	
ICR mice (F)	PFOA, 0 or 10 mg/kg/day, 14 days, oral	↓ Serum testosterone concentration	Wang et al. (2018b)
Kunming mice (PF)	PFOA, 0, 1, 2.5, or 5.0 mg/kg/day, GD 1–17, oral	↓ Serum testosterone concentration in male offspring mice at $\geq 1$ mg/kg/day; except on PND7, ↓ at 1 mg/kg/day	Song et al. (2018)
CD-1 mice (F)	PFOA, 0, 1, 5, 10 or 20 mg/kg/day, 10 days, oral	↑ Serum testosterone concentration at 1 mg/kg only.	Yang et al. (2022)
CrI:CD rat (M)	PFOA, 0 or 300 ppm, 3 to 24 months, diet	↑ Serum testosterone concentration at 6 months only.	Biegel et al. (2001)
Sprague-Dawley rat (M)	PFOS, 0, 20, or 100 ppm, 7 days, diet	↑ Liver testosterone 6 $\beta$ -hydroxylase activity at 100 ppm.	Elcombe et al. (2012a)
Sprague-Dawley rat (M)	PFOS, 0, 20, or 100 ppm, up to 28 days, diet	↑ Liver testosterone 6 $\beta$ -hydroxylase activity at $\geq 20$ ppm at 28 days.	Elcombe et al. (2012b)
Wistar rat (M)	PFOA: 0 or 5 mg/kg/day for 4 wk, oral	↓ Serum testosterone concentration.	Owumi et al. (2021b)
CrI: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 21 weeks, oral	No effect on serum testosterone concentration.	Perkins et al. (2004)
<b><i>Pituitary hormone effects (LH, FSH, PRL)</i></b>			
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 weeks, oral	No effect on serum FSH or LH concentrations.	Huang et al. (2022a)
CD-1 mice (PF)	PFOS, 0, 0.5, 2.0 or 8.0 mg/kg/day, GD 11–16, oral	↓ Maternal serum mPLP-C $\alpha$ and mPLP-K at $\geq 0.5$ mg/kg.	Lee et al. (2015b)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
CD-1 mice (M)	PFOS, 0, 1, or 5 mg/kg/day, 21 days, oral	↓ Maternal serum mPL-II at $\geq 2$ mg/kg. ↓ Serum LH at 5 mg/kg/day, no effect on serum FSH.	Li et al. (2022e)
ICR mice (M)	PFOS, 0, 0.5, 5, or 10 mg/kg/day, 4 weeks, oral	No effect on serum LH or FSH concentrations.	Qiu et al. (2021)
CD-1 mice (M)	PFOS, 0, 1, 5, or 10 mg/kg/day, up to 21 days, oral	↓ Testicular mRNA for growth hormone receptor at 5 (not significant) and at 10 mg/kg/day.	Wan et al. (2011)
ICR mice (F)	PFOS, 0 or 10 mg/kg/day, 30 days, oral	↓ Serum LH concentration.	Wang et al. (2018b)
Wistar rat (M)	PFOS, 0, 0.015, or 0.15 mg/kg/d, 60 days, oral	↓ Testicular LHR mRNA at 0.15 mg/kg/day.	Alam et al. (2021)
Sprague-Dawley rat (M)	PFOS, 0, 5; or 10, mg/kg/day, 21 days, oral	No effect on serum LH or FSH concentrations.	Li et al. (2018d)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↑ Hypothalamic LH mRNA at 0.5 and 3 mg/kg/day. ↑ Hypothalamic FSH mRNA at 0.5 and 1 mg/kg/day. ↓ Serum LH concentration at $\geq 0.5$ mg/kg/day. ↑ FSH concentration at $\geq 0.5$ mg/kg/day.	López-Doval et al. (2014)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Serum LH concentration at $\geq 0.5$ mg/kg/day.	López-Doval et al. (2015)
Sprague-Dawley rat (M)	PFOS, 0 or 20 mg/kg/day, 56 days, oral	↓ Serum LH and FSH concentration.	Umar Ijaz et al. (2022)
CD-1 mice (PF)	PFOA, 0, 2, 10, or 25 mg/kg/day, GD 11–16, oral	↓ Placental mPLP-II, mPLP-E, and mPLP-E mRNA at $\geq 2$ mg/kg.	Suh et al. (2011)
ICR mice (F)	PFOA, 0, 0.5, 2, or 5 mg/kg/day, 28 days, oral	↓ Serum LH concentration at $\geq 2$ mg/kg/day.	Zhang et al. (2020b)



**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
CD rat (M)	PFOA, 0 or 300 ppm, 3 to 24 months, oral	↑ Serum LH concentrations at 6 and 18 months only. ↑ Serum FSH concentration at 6 months only. ↓ Serum prolactin concentration at 3 and 6 months only.	Biegel et al. (2001)
CrI:CD rat (M)	Ammonium perfluorooctanoate (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	No effect on serum LH concentration.	Perkins et al. (2004)
Wistar rat (M)	PFOA: 0 or 5 mg/kg/day for 4 weeks, oral	↓ Serum FSH ↓ Serum LH	Owumi et al. (2021b)
<i>Other hormone effects</i>			
CD-1 mice (PF)	PFOS, 0, 1.5, 3, or 6 mg/kg/day, GD 6–18, oral	No change in maternal serum corticosterone concentration.	Fuentes et al. (2006)
CD-1 mice (M)	PFOS, 0, 1, 5, or 10 mg/kg/day, up to 21 days, oral	↓ Testicular mRNA for growth hormone receptor GHR and insulin-like growth factor 1 receptor at ≥ 5 mg/kg/day.	Wan et al. (2011)
CD-1 mice (PF)	PFOS, 0, 0.3 or 3.0 mg/kg/day, GD 1–PND 21, oral	↑ Fasting serum insulin in PND 63 offspring at ≥ 3 mg/kg/day.	Wan et al. (2014)
ICR mice (F)	PFOS, 0 or 10 mg/kg/day, 14 days, oral	↓ Serum progesterone, ↓ Serum GnRH, ↓ Serum corticosteroid	Wang et al. (2018b)
Wistar rat (M)	PFOS, 0, 0.015, or 0.15 mg/kg/day, 60 days, oral	↑ Serum progesterone concentrations at ≥ 0.015 mg/kg/day.	Alam et al. (2021)
Wistar (M)	PFOA, 0, 0.015, or 0.15 mg/kg/day, 2 months, oral	↑ Serum progesterone concentration at ≥ 0.015 mg/kg/day.	Han et al. (2022)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Hypothalamic GnRH mRNA at $\geq 0.5$ mg/kg, ↓ GnRH level at 1 and 3 mg/kg/day, ↑ GnRH level at 6 mg/kg/day.	López-Doval et al. (2014)
Sprague-Dawley rat (M)	PFOS, 0, 0.5; 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Hypothalamus GnRH at 1 and 3 mg/kg/day. ↑ Hypothalamus GnRH at 6 mg/kg/day.	López-Doval et al. (2015)
Sprague-Dawley rat (M)	PFOS, 0, 1.0; 3.0, or 6.0 mg/kg/day, 28 days, oral	↓ Pituitary GnRH protein at $\geq 1$ mg/kg/day, ↓ testis GnRH mRNA at $\geq 1$ mg/kg/day, ↑ testis GnRH protein at $\geq 1$ mg/kg/day	López-Doval et al. (2016)
Wistar rat (PF)	PFOS, 0, 0.5; or 1.5 mg/kg/day, GD 0–PND 21, oral	↑ Pup serum insulin and leptin at 18 weeks at 1.5 mg/kg/day.	Lv et al. (2013)
Sprague-Dawley rat (M)	PFOS, 0, 0.5, 1.0, 3.0, or 6.0 mg/kg/day, 28 days	↓ Adrenal gland weight, ↓ Serum corticosterone at $\geq 0.5$ mg/kg/day, ↓ Serum ACTH at $\geq 0.5$ mg/kg/day, ↓ hypothalamus CRH at $\geq 0.5$ mg/kg/day, ↑ adrenal ACTH receptor mRNA at $\geq 1$ mg/kg/day	Pereiro et al. (2014)
Balb/c mice (M)	PFOA, 0, 1, or 5 mg/kg/day, 3 weeks, oral	↑ Serum insulin concentrations at $\geq 1$ mg/kg/day. ↓ Serum leptin concentration at $\geq 1$ mg/kg/day. ↓ Serum adiponectin concentration at 5 mg/kg/day.	Du et al. (2018)
CD-1 mice (PF)	PFOA, 0, 0.01, 0.1, 0.3, 1, 3, or 5 mg/kg/day, GD 1–17, oral	↑ Serum insulin and leptin concentrations at 0.01 and 0.1 mg/kg at 21–33 weeks of age.	Hines et al. (2009)
Balb/c mice (M)	PFOA, 0, 1.25, 5, or 20 mg/kg/day, 28 days, oral	↑ Serum corticosterone concentration at $\geq 5$ mg/kg/day. ↓ Serum ACTH concentration at 20 mg/kg/day.	Sun et al. (2018)

**Table S4.26 End-points relevant to modulation of receptor-mediated effects (endocrine) in experimental systems in vivo exposed to PFOA and PFOS**

Species, strain, sex	Dosing regimen	Relevant finding	Reference
CD-1 mice (PF) C57Bl/6 mice (PF)	PFOA, 0, 0.01, 0.1, 0.3 or 1.0 mg/kg/day, GD 1–17, oral	No effect on female offspring serum progesterone concentration.	Tucker et al. (2015)
Kunming mice (M)	PFOA or 5.0 mg/kg, oral	No effect on serum insulin concentration.	Wu et al. (2017)
CD-1 mice (F)	PFOA, 0, 1, 5, 10 or 20 mg/kg/day, 10 days, oral	↓ Serum progesterone and pregnenolone concentrations at 5 mg/kg only.	Yang et al. (2022)
ICR mice (F)	PFOA, 0, 0.5, 2, or 5 mg/kg/day, 28 days, oral	↓ Hypothalamic GnRH at ≥ 2 mg/kg/day ↓ serum progesterone concentration at ≥ 2 mg/kg/day.	Zhang et al. (2020b)
C57Bl/6 mice (F)	PFOA, 0 or 5 mg/kg/day, 4 weeks, oral	↑ Serum progesterone concentration.	Zhao et al. (2010)
Wistar rat (PF)	PFOA, 0 or 20 mg/kg/day, 14 days (GD7-GD21), oral	No effect on plasma insulin or leptin concentration on GD21.	Boberg et al. (2008)
Sprague-Dawley rat (F)	PFOA, 0 or 0.01 mg/kg/day, 21 days, oral	No effect on serum progesterone concentration.	Su et al. (2022a)

ACTH, adrenocorticotropic hormone; APFO, ammonium perfluorooctanoate; AR, androgen receptor; bw, body weight; CRH, corticotrophin-releasing hormone; d, day(s); F, female; FSH, follicle-stimulating hormone; FT4, free thyroxine; GD, gestational day; GHR, growth hormone receptor; GnRH, gonadotropin-releasing hormone; hPPAR $\alpha$ , humanized PPAR $\alpha$ ; IP, intraperitoneal; LH, luteinizing hormone; M, male; mPL-II, mouse placental lactogen, mPLP-C $\alpha$ , mouse prolactin-like protein C $\alpha$ ; mPLP-K, mouse prolactin-like protein K; NS, not specified; PF, pregnant female; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PND, postnatal day; PPAR, peroxisome proliferator-activated receptor; ppm, parts per million; PXR, pregnane X receptor; PRL, prolactin; rT3, reverse triiodothyronine; TH, thyroid hormone; Thrsp, thyroid hormone responsive protein; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone (thyrotropin); TT4, thyroxine; total thyroxine; wk, week(s); WT, wildtype.

## References

- Abbott BD, Wood CR, Watkins AM, Tatum-Gibbs K, Das KP, Lau C (2012). Effects of perfluorooctanoic acid (PFOA) on expression of peroxisome proliferator-activated receptors (PPAR) and nuclear receptor-regulated genes in fetal and postnatal CD-1 mouse tissues. *Reprod Toxicol.* 33(4):491–505. <https://doi.org/10.1016/j.reprotox.2011.11.005> PMID:22154759
- Abe T, Takahashi M, Kano M, Amaike Y, Ishii C, Maeda K, et al. (2017). Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid. *Arch Toxicol.* 91(6):2365–74. <https://doi.org/10.1007/s00204-016-1888-3> PMID:27832320

- Aimuzi R, Luo K, Chen Q, Wang H, Feng L, Ouyang F, et al. (2019). Perfluoroalkyl and polyfluoroalkyl substances and fetal thyroid hormone levels in umbilical cord blood among newborns by prelabor caesarean delivery. *Environ Int.* 130:104929. <https://doi.org/10.1016/j.envint.2019.104929> PMID:31228788
- Aimuzi R, Luo K, Huang R, Huo X, Nian M, Ouyang F, et al.; Shanghai Birth Cohort Study (2020). Perfluoroalkyl and polyfluoroalkyl substances and maternal thyroid hormones in early pregnancy. *Environ Pollut.* 264:114557. <https://doi.org/10.1016/j.envpol.2020.114557> PMID:32388293
- Alam MN, Han X, Nan B, Liu L, Tian M, Shen H, et al. (2021). Chronic low-level perfluorooctane sulfonate (PFOS) exposure promotes testicular steroidogenesis through enhanced histone acetylation. *Environ Pollut.* 284:117518. <https://doi.org/10.1016/j.envpol.2021.117518> PMID:34261222
- Albrecht PP, Torsell NE, Krishnan P, Ehresman DJ, Frame SR, Chang SC, et al. (2013). A species difference in the peroxisome proliferator-activated receptor  $\alpha$ -dependent response to the developmental effects of perfluorooctanoic acid. *Toxicol Sci.* 131(2):568–82. <https://doi.org/10.1093/toxsci/kfs318> PMID:23143925
- Arbuckle TE, MacPherson S, Foster WG, Sathyanarayana S, Fisher M, Monnier P, et al. (2020). Prenatal perfluoroalkyl substances and newborn anogenital distance in a Canadian cohort. *Reprod Toxicol.* 94:31–9. <https://doi.org/10.1016/j.reprotox.2020.03.011> PMID:32283250
- Attema B, Janssen AWF, Rijkers D, van Schothorst EM, Hooiveld GJEJ, Kersten S (2022). Exposure to low-dose perfluorooctanoic acid promotes hepatic steatosis and disrupts the hepatic transcriptome in mice. *Mol Metab.* 66:101602. <https://doi.org/10.1016/j.molmet.2022.101602> PMID:36115532
- Barrett ES, Chen C, Thurston SW, Haug LS, Sabaredzovic A, Fjeldheim FN, et al. (2015). Perfluoroalkyl substances and ovarian hormone concentrations in naturally cycling women. *Fertil Steril.* 103(5):1261–70.e3. <https://doi.org/10.1016/j.fertnstert.2015.02.001> PMID:25747128
- Behnisch PA, Besselink H, Weber R, Willand W, Huang J, Brouwer A (2021). Developing potency factors for thyroid hormone disruption by PFASs using TTR-TR $\beta$  CALUX<sup>®</sup> bioassay and assessment of PFASs mixtures in technical products. *Environ Int.* 157:106791. <https://doi.org/10.1016/j.envint.2021.106791> PMID:34364217
- Behr A-C, Kwiatkowski A, Ståhlman M, Schmidt FF, Luckert C, Braeuning A, et al. (2020a). Impairment of bile acid metabolism by perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in human HepaRG hepatoma cells. *Arch Toxicol.* 94(5):1673–86. <https://doi.org/10.1007/s00204-020-02732-3> PMID:32253466
- Behr AC, Lichtenstein D, Braeuning A, Lampen A, Buhrke T (2018). Perfluoroalkylated substances (PFAS) affect neither estrogen and androgen receptor activity nor steroidogenesis in human cells in vitro. *Toxicol Lett.* 291:51–60. <https://doi.org/10.1016/j.toxlet.2018.03.029> PMID:29601859
- Behr AC, Plinsch C, Braeuning A, Buhrke T (2020b). Activation of human nuclear receptors by perfluoroalkylated substances (PFAS). *Toxicol In Vitro.* 62:104700. <https://doi.org/10.1016/j.tiv.2019.104700> PMID:31676336
- Benninghoff AD, Bisson WH, Koch DC, Ehresman DJ, Kolluri SK, Williams DE (2011). Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. *Toxicol Sci.* 120(1):42–58. <https://doi.org/10.1093/toxsci/kfq379> PMID:21163906
- Berg V, Nøst TH, Hansen S, Elverland A, Veyhe A-S, Jorde R, et al. (2015). Assessing the relationship between perfluoroalkyl substances, thyroid hormones and binding proteins in pregnant women; a longitudinal mixed effects approach. *Environ Int.* 77:63–9. <https://doi.org/10.1016/j.envint.2015.01.007> PMID:25647630
- Bérubé R, LeFauve MK, Heldman S, Chiang Y-TT, Birbeck J, Westrick J, et al. (2023). Adipogenic and endocrine disrupting mixture effects of organic and inorganic pollutant mixtures. *Sci Total Environ.* 876:162587. <https://doi.org/10.1016/j.scitotenv.2023.162587> PMID:36871739

- 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(1):44–55. <https://doi.org/10.1093/toxsci/60.1.44> PMID:11222872
- Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, et al. (2011). Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE\*3-Leiden CETP mice. *Toxicol Sci.* 123(1):290–303. <https://doi.org/10.1093/toxsci/kfr142> PMID:21705711
- Bischel HN, Macmanus-Spencer LA, Luthy RG (2010). Noncovalent interactions of long-chain perfluoroalkyl acids with serum albumin. *Environ Sci Technol.* 44(13):5263–9. <https://doi.org/10.1021/es101334s> PMID:20540534
- Bjork JA, Butenhoff JL, Wallace KB (2011). Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. *Toxicology.* 288(1–3):8–17. <https://doi.org/10.1016/j.tox.2011.06.012> PMID:21723365
- Bjork JA, Wallace KB (2009). Structure–activity relationships and human relevance for perfluoroalkyl acid-induced transcriptional activation of peroxisome proliferation in liver cell cultures. *Toxicol Sci.* 111(1):89–99. <https://doi.org/10.1093/toxsci/kfp093> PMID:19407336
- Blake BE, Cope HA, Hall SM, Keys RD, Mahler BW, McCord J, et al. (2020). Evaluation of maternal, embryo, and placental effects in CD-1 mice following gestational exposure to perfluorooctanoic acid (PFOA) or hexafluoropropylene oxide dimer acid (HFPO-DA or GenX). *Environ Health Perspect.* 128(2):27006. <https://doi.org/10.1289/EHP6233> PMID:32074459
- Blake BE, Pinney SM, Hines EP, Fenton SE, Ferguson KK (2018). Associations between longitudinal serum perfluoroalkyl substance (PFAS) levels and measures of thyroid hormone, kidney function, and body mass index in the Fernald Community Cohort. *Environ Pollut.* 242(Pt A):894–904. <https://doi.org/10.1016/j.envpol.2018.07.042> PMID:30373035
- Bloom MS, Kannan K, Spliethoff HM, Tao L, Aldous KM, Vena JE (2010). Exploratory assessment of perfluorinated compounds and human thyroid function. *Physiol Behav.* 99(2):240–5. <https://doi.org/10.1016/j.physbeh.2009.02.005> PMID:19419669
- Boberg J, Metzдорff S, Wortziger R, Axelstad M, Brokken L, Vinggaard AM, et al. (2008). Impact of diisobutyl phthalate and other PPAR agonists on steroidogenesis and plasma insulin and leptin levels in fetal rats. *Toxicology.* 250(2–3):75–81. <https://doi.org/10.1016/j.tox.2008.05.020> PMID:18602967
- Buhrke T, Kibellus A, Lampen A (2013). In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths. *Toxicol Lett.* 218(2):97–104. <https://doi.org/10.1016/j.toxlet.2013.01.025> PMID:23391484
- Buhrke T, Krüger E, Pevny S, Rößler M, Bitter K, Lampen A (2015). Perfluorooctanoic acid (PFOA) affects distinct molecular signalling pathways in human primary hepatocytes. *Toxicology.* 333:53–62. <https://doi.org/10.1016/j.tox.2015.04.004> PMID:25868421
- Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, et al. (2002). Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicol Sci.* 69(1):244–57. <https://doi.org/10.1093/toxsci/69.1.244> PMID:12215680
- Butenhoff JL, Kennedy GL Jr, Chang SC, Olsen GW (2012a). Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. *Toxicology.* 298(1–3):1–13. <https://doi.org/10.1016/j.tox.2012.04.001> PMID:22531602

- Byrne SC, Miller P, Seguinot-Medina S, Waghiyi V, Buck CL, von Hippel FA, et al. (2018). Exposure to perfluoroalkyl substances and associations with serum thyroid hormones in a remote population of Alaska natives. *Environ Res.* 166:537–43. <https://doi.org/10.1016/j.envres.2018.06.014> PMID:29958161
- Caron-Beaudoin É, Ayotte P, Laouan Sidi EA, Gros-Louis McHugh N, Lemire M; Community of Lac Simon; Community of Winneway–Long Point First Nation; CSSS Tshukuminu Kanani of Nutashkuan; Community of Unamen Shipu (2019). Exposure to perfluoroalkyl substances (PFAS) and associations with thyroid parameters in First Nation children and youth from Quebec. *Environ Int.* 128:13–23. <https://doi.org/10.1016/j.envint.2019.04.029> PMID:31029975
- Caserta D, Ciardo F, Bordi G, Guerranti C, Fanello E, Perra G, et al. (2013). Correlation of endocrine disrupting chemicals serum levels and white blood cells gene expression of nuclear receptors in a population of infertile women. *Int J Endocrinol.* 2013:510703. <https://doi.org/10.1155/2013/510703> PMID:23710174
- Chang CJ, Barr DB, Zhang Q, Dunlop AL, Smarr MM, Kannan K, et al. (2021). Associations of single and multiple per- and polyfluoroalkyl substance (PFAS) exposure with vitamin D biomarkers in African American women during pregnancy. *Environ Res.* 202:111713. <https://doi.org/10.1016/j.envres.2021.111713> PMID:34284018
- Chang S, Allen BC, Andres KL, Ehresman DJ, Falvo R, Provencher A, et al. (2017). Evaluation of serum lipid, thyroid, and hepatic clinical chemistries in association with serum perfluorooctanesulfonate (PFOS) in cynomolgus monkeys after oral dosing with potassium PFOS. *Toxicol Sci.* 156(2):387–401. <https://doi.org/10.1093/toxsci/kfw267> PMID:28115654
- Chang S-C, Ehresman DJ, Bjork JA, Wallace KB, Parker GA, Stump DG, et al. (2009). Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: toxicokinetics, thyroid hormone status, and related gene expression. *Reprod Toxicol.* 27(3–4):387–99. <https://doi.org/10.1016/j.reprotox.2009.01.005> PMID:19429409
- Chang SC, Thibodeaux JR, Eastvold ML, Ehresman DJ, Bjork JA, Froehlich JW, et al. (2007). Negative bias from analog methods used in the analysis of free thyroxine in rat serum containing perfluorooctanesulfonate (PFOS). *Toxicology.* 234(1–2):21–33. <https://doi.org/10.1016/j.tox.2007.01.020> PMID:17368689
- Chang SC, Thibodeaux JR, Eastvold ML, Ehresman DJ, Bjork JA, Froehlich JW, et al. (2008). Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). *Toxicology.* 243(3):330–9. <https://doi.org/10.1016/j.tox.2007.10.014> PMID:18063289
- Chen YM, Guo LH (2009). Fluorescence study on site-specific binding of perfluoroalkyl acids to human serum albumin. *Arch Toxicol.* 83(3):255–61. <https://doi.org/10.1007/s00204-008-0359-x> PMID:18854981
- Cheng X, Klaassen CD (2008). Perfluorocarboxylic acids induce cytochrome P450 enzymes in mouse liver through activation of PPAR-alpha and CAR transcription factors. *Toxicol Sci.* 106(1):29–36. <https://doi.org/10.1093/toxsci/kfn147> PMID:18648086
- Conley JM, Lambright CS, Evans N, Medlock-Kakaley E, Hill D, McCord J, et al. (2022). Developmental toxicity of Nafion byproduct 2 (NBP2) in the Sprague-Dawley rat with comparisons to hexafluoropropylene oxide-dimer acid (HFPO-DA or GenX) and perfluorooctane sulfonate (PFOS). *Environ Int.* 160:107056. <https://doi.org/10.1016/j.envint.2021.107056> PMID:34952357
- Corsini E, Avogadro A, Galbiati V, dell'Agli M, Marinovich M, Galli CL, et al. (2011). In vitro evaluation of the immunotoxic potential of perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol.* 250(2):108–16. <https://doi.org/10.1016/j.taap.2010.11.004> PMID:21075133
- Corsini E, Sangiovanni E, Avogadro A, Galbiati V, Viviani B, Marinovich M, et al. (2012). In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol.* 258(2):248–55. <https://doi.org/10.1016/j.taap.2011.11.004> PMID:22119708

- Crawford NM, Fenton SE, Strynar M, Hines EP, Pritchard DA, Steiner AZ (2017). Effects of perfluorinated chemicals on thyroid function, markers of ovarian reserve, and natural fertility. *Reprod Toxicol.* 69:53–9. <https://doi.org/10.1016/j.reprotox.2017.01.006> PMID:28111093
- Cui Q, Pan Y, Wang J, Liu H, Yao B, Dai J (2020). Exposure to per- and polyfluoroalkyl substances (PFASs) in serum versus semen and their association with male reproductive hormones. *Environ Pollut.* 266(Pt 2):115330. <https://doi.org/10.1016/j.envpol.2020.115330> PMID:32781340
- Curran I, Hierlihy SL, Liston V, Pantazopoulos P, Nunnikhoven A, Tittlemier S, et al. (2008). Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *J Toxicol Environ Health A.* 71(23):1526–41. <https://doi.org/10.1080/15287390802361763> PMID:18923995
- Dallaire R, Dewailly E, Pereg D, Dery S, Ayotte P (2009). Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. *Environ Health Perspect.* 117(9):1380–6. <https://doi.org/10.1289/ehp.0900633> PMID:19750101
- Davidson N, Ramhøj L, Lykkebo CA, Kugathas I, Poulsen R, Rosenmai AK, et al. (2022). PFOS-induced thyroid hormone system disrupted rats display organ-specific changes in their transcriptomes. *Environ Pollut.* 305:119340. <https://doi.org/10.1016/j.envpol.2022.119340> PMID:35460815
- de Cock M, de Boer MR, Lamoree M, Legler J, van de Bor M (2014). Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants – a Dutch prospective cohort study. *Environ Health.* 13(1):106. <https://doi.org/10.1186/1476-069X-13-106> PMID:25495114
- Derakhshan A, Kortenkamp A, Shu H, Broeren MAC, Lindh CH, Peeters RP, et al. (2022). Association of per- and polyfluoroalkyl substances with thyroid homeostasis during pregnancy in the SELMA study. *Environ Int.* 167:107420. <https://doi.org/10.1016/j.envint.2022.107420> PMID:35870378
- Di Nisio A, Rocca MS, De Toni L, Sabovic I, Guidolin D, Dall'Acqua S, et al. (2020). Endocrine disruption of vitamin D activity by perfluoro-octanoic acid (PFOA). *Sci Rep.* 10(1):16789. <https://doi.org/10.1038/s41598-020-74026-8> PMID:33033332
- Dong H, Curran I, Williams A, Bondy G, Yauk CL, Wade MG (2016). Hepatic miRNA profiles and thyroid hormone homeostasis in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *Environ Toxicol Pharmacol.* 41:201–10. <https://doi.org/10.1016/j.etap.2015.12.009> PMID:26724606
- Dreyer AF, Jensen RC, Glinborg D, Schmedes AV, Brandslund I, Nielsen F, et al. (2020). Perfluoroalkyl substance exposure early in pregnancy was negatively associated with late pregnancy cortisone levels. *J Clin Endocrinol Metab.* 105(8):dgaa292. <https://doi.org/10.1210/clinem/dgaa292> PMID:32436946
- Du G, Hu J, Huang H, Qin Y, Han X, Wu D, et al. (2013). Perfluorooctane sulfonate (PFOS) affects hormone receptor activity, steroidogenesis, and expression of endocrine-related genes in vitro and in vivo. *Environ Toxicol Chem.* 32(2):353–60. <https://doi.org/10.1002/etc.2034> PMID:23074026
- Du G, Sun J, Zhang Y (2018). Perfluorooctanoic acid impaired glucose homeostasis through affecting adipose AKT pathway. *Cytotechnology.* 70(1):479–87. <https://doi.org/10.1007/s10616-017-0164-6> PMID:29335808
- Dufour P, Pirard C, Petrossians P, Beckers A, Charlier C (2020). Association between mixture of persistent organic pollutants and thyroid pathologies in a Belgian population. *Environ Res.* 181:108922. <https://doi.org/10.1016/j.envres.2019.108922> PMID:31759644

- Elcombe CR, Elcombe BM, Foster JR, Chang SC, Ehresman DJ, Butenhoff JL (2012b). Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPAR $\alpha$  and CAR/PXR. *Toxicology*. 293(1–3):16–29. <https://doi.org/10.1016/j.tox.2011.12.014> PMID:22245121
- Elcombe CR, Elcombe BM, Foster JR, Chang SC, Ehresman DJ, Noker PE, et al. (2012a). Evaluation of hepatic and thyroid responses in male Sprague-Dawley rats for up to eighty-four days following seven days of dietary exposure to potassium perfluorooctanesulfonate. *Toxicology*. 293(1–3):30–40. <https://doi.org/10.1016/j.tox.2011.12.015> PMID:22239858
- Etzel TM, Braun JM, Buckley JP (2019). Associations of serum perfluoroalkyl substance and vitamin D biomarker concentrations in NHANES, 2003–2010. *Int J Hyg Environ Health*. 222(2):262–9. <https://doi.org/10.1016/j.ijheh.2018.11.003> PMID:30503928
- Evans N, Conley JM, Cardon M, Hartig P, Medlock-Kakaley E, Gray LEJ Jr (2022). In vitro activity of a panel of per- and polyfluoroalkyl substances (PFAS), fatty acids, and pharmaceuticals in peroxisome proliferator-activated receptor (PPAR) alpha, PPAR gamma, and estrogen receptor assays. *Toxicol Appl Pharmacol*. 449:116136. <https://doi.org/10.1016/j.taap.2022.116136> PMID:35752307
- Fedorenko M, Alesio J, Fedorenko A, Slitt A, Bothun GD (2021). Dominant entropic binding of perfluoroalkyl substances (PFASs) to albumin protein revealed by  $^{19}\text{F}$  NMR. *Chemosphere*. 263:128083. <https://doi.org/10.1016/j.chemosphere.2020.128083> PMID:33297081
- Fletcher T, Galloway TS, Melzer D, Holcroft P, Cipelli R, Pilling LC, et al. (2013). Associations between PFOA, PFOS and changes in the expression of genes involved in cholesterol metabolism in humans. *Environ Int*. 57–58:2–10. <https://doi.org/10.1016/j.envint.2013.03.008> PMID:23624243
- Franco ME, Sutherland GE, Fernandez-Luna MT, Lavado R (2020). Altered expression and activity of phase I and II biotransformation enzymes in human liver cells by perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS). *Toxicology*. 430:152339. <https://doi.org/10.1016/j.tox.2019.152339> PMID:31809754
- Fuentes S, Colomina MT, Rodriguez J, Vicens P, Domingo JL (2006). Interactions in developmental toxicology: concurrent exposure to perfluorooctane sulfonate (PFOS) and stress in pregnant mice. *Toxicol Lett*. 164(1):81–9. <https://doi.org/10.1016/j.toxlet.2005.11.013> PMID:16384669
- Gallo E, Barbiellini Amidei C, Barbieri G, Fabricio ASC, Gion M, Pitter G, et al. (2022). Perfluoroalkyl substances and thyroid stimulating hormone levels in a highly exposed population in the Veneto Region. *Environ Res*. 203:111794. <https://doi.org/10.1016/j.envres.2021.111794> PMID:34358507
- Galloway TS, Fletcher T, Thomas OJ, Lee BP, Pilling LC, Harries LW (2015). PFOA and PFOS are associated with reduced expression of the parathyroid hormone 2 receptor (PTH2R) gene in women. *Chemosphere*. 120:555–62. <https://doi.org/10.1016/j.chemosphere.2014.09.066> PMID:25462297
- Gao Y, Guo X, Wang S, Chen F, Ren X, Xiao H, et al. (2020). Perfluorooctane sulfonate enhances mRNA expression of PPAR $\gamma$  and ap2 in human mesenchymal stem cells monitored by long-retained intracellular nanosensor. *Environ Pollut*. 263(Pt B):114571. <https://doi.org/10.1016/j.envpol.2020.114571> PMID:32320904
- Garoché C, Boulahtouf A, Grimaldi M, Chiavarina B, Toporova L, den Broeder MJ, et al. (2021). Interspecies differences in activation of peroxisome proliferator-activated receptor  $\gamma$  by pharmaceutical and environmental chemicals. *Environ Sci Technol*. 55(24):16489–501. <https://doi.org/10.1021/acs.est.1c04318> PMID:34843233
- Gorrochategui E, Pérez-Albaladejo E, Casas J, Lacorte S, Porte C (2014). Perfluorinated chemicals: differential toxicity, inhibition of aromatase activity and alteration of cellular lipids in human placental cells. *Toxicol Appl Pharmacol*. 277(2):124–30. <https://doi.org/10.1016/j.taap.2014.03.012> PMID:24680846



- Goudarzi H, Araki A, Itoh S, Sasaki S, Miyashita C, Mitsui T, et al. (2017b). The association of prenatal exposure to perfluorinated chemicals with glucocorticoid and androgenic hormones in cord blood samples: the Hokkaido Study. *Environ Health Perspect*. 125(1):111–8. <https://doi.org/10.1289/EHP142> PMID:27219028
- Guo J, Zhang J, Wang Z, Zhang L, Qi X, Zhang Y, et al. (2021c). Umbilical cord serum perfluoroalkyl substance mixtures in relation to thyroid function of newborns: findings from Sheyang Mini Birth Cohort Study. *Chemosphere*. 273:129664. <https://doi.org/10.1016/j.chemosphere.2021.129664> PMID:33493812
- Han X, Alam MN, Cao M, Wang X, Cen M, Tian M, et al. (2022). Low levels of perfluorooctanoic acid exposure activates steroid hormone biosynthesis through repressing histone methylation in rats. *Environ Sci Technol*. 56(9):5664–72. <https://doi.org/10.1021/acs.est.1c08885> PMID:35438966
- Han X, Snow TA, Kemper RA, Jepson GW (2003). Binding of perfluorooctanoic acid to rat and human plasma proteins. *Chem Res Toxicol*. 16(6):775–81. <https://doi.org/10.1021/tx034005w> PMID:12807361
- Harlow SD, Hood MM, Ding N, Mukherjee B, Calafat AM, Randolph JF Jr, et al. (2021). Per- and polyfluoroalkyl substances and hormone levels during the menopausal transition. *J Clin Endocrinol Metab*. 106(11):e4427–37. <https://doi.org/10.1210/clinem/dgab476> PMID:34181018
- Heffernan AL, Cunningham TK, Drage DS, Aylward LL, Thompson K, Vijayasarathy S, et al. (2018). Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters. *Int J Hyg Environ Health*. 221(7):1068–75. <https://doi.org/10.1016/j.ijheh.2018.07.009> PMID:30037723
- Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE (2009). Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Mol Cell Endocrinol*. 304(1–2):97–105. <https://doi.org/10.1016/j.mce.2009.02.021> PMID:19433254
- Houck KA, Patlewicz G, Richard AM, Williams AJ, Shobair MA, Smeltz M, et al. (2021). Bioactivity profiling of per- and polyfluoroalkyl substances (PFAS) identifies potential toxicity pathways related to molecular structure. *Toxicology*. 457:152789. <https://doi.org/10.1016/j.tox.2021.152789> PMID:33887376
- Huang J, Ren H, Chen A, Li T, Wang H, Jiang L, et al. (2022a). Perfluorooctane sulfonate induces suppression of testosterone biosynthesis via Sertoli cell-derived exosomal/miR-9–3p downregulating StAR expression in Leydig cells. *Environ Pollut*. 301:118960. <https://doi.org/10.1016/j.envpol.2022.118960> PMID:35150797
- Inoue K, Ritz B, Andersen SL, Ramlau-Hansen CH, Høyer BB, Bech BH, et al. (2019). Perfluoroalkyl substances and maternal thyroid hormones in early pregnancy; findings in the Danish National Birth Cohort. *Environ Health Perspect*. 127(11):117002. <https://doi.org/10.1289/EHP5482> PMID:31714155
- Ishibashi H, Hirano M, Kim EY, Iwata H (2019). In vitro and in silico evaluations of binding affinities of perfluoroalkyl substances to Baikal seal and human peroxisome proliferator-activated receptor  $\alpha$ . *Environ Sci Technol*. 53(4):2181–8. <https://doi.org/10.1021/acs.est.8b07273> PMID:30649875
- Itoh S, Araki A, Mitsui T, Miyashita C, Goudarzi H, Sasaki S, et al. (2016). Association of perfluoroalkyl substances exposure in utero with reproductive hormone levels in cord blood in the Hokkaido Study on Environment and Children’s Health. *Environ Int*. 94:51–9. <https://doi.org/10.1016/j.envint.2016.05.011> PMID:27209000
- Itoh S, Araki A, Miyashita C, Yamazaki K, Goudarzi H, Minatoya M, et al. (2019). Association between perfluoroalkyl substance exposure and thyroid hormone/thyroid antibody levels in maternal and cord blood: the Hokkaido Study. *Environ Int*. 133(Pt A):105139. <https://doi.org/10.1016/j.envint.2019.105139> PMID:31518930

- Jain RB (2013). Association between thyroid profile and perfluoroalkyl acids: data from NHANES 2007–2008. *Environ Res.* 126:51–9. <https://doi.org/10.1016/j.envres.2013.08.006> PMID:24053974
- Jensen RC, Glintborg D, Gade Timmermann CA, Nielsen F, Kyhl HB, Frederiksen H, et al.; The Odense Child Cohort (2020). Prenatal exposure to perfluorodecanoic acid is associated with lower circulating concentration of adrenal steroid metabolites during mini puberty in human female infants. *Environ Res.* 182:109101. <https://doi.org/10.1016/j.envres.2019.109101> PMID:32069767
- Jensen RC, Glintborg D, Timmermann CAG, Nielsen F, Boye H, Madsen JB, et al.; The Odense Child Cohort (2022). Higher free thyroxine associated with PFAS exposure in first trimester. *Environ Res.* 212(Pt D):113492. <https://doi.org/10.1016/j.envres.2022.113492> PMID:35597289
- Ji K, Kim S, Kho Y, Paek D, Sakong J, Ha J, et al. (2012). Serum concentrations of major perfluorinated compounds among the general population in Korea: dietary sources and potential impact on thyroid hormones. *Environ Int.* 45:78–85. <https://doi.org/10.1016/j.envint.2012.03.007> PMID:22580293
- Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jørgensen N (2009). Do perfluoroalkyl compounds impair human semen quality? *Environ Health Perspect.* 117(6):923–7. <https://doi.org/10.1289/ehp.0800517> PMID:19590684
- Joensen UN, Veyrand B, Antignac J-P, Blomberg Jensen M, Petersen JH, Marchand P, et al. (2013). PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men. *Hum Reprod.* 28(3):599–608. <https://doi.org/10.1093/humrep/des425> PMID:23250927
- Kang H, Lee HK, Moon HB, Kim S, Lee J, Ha M, et al. (2018). Perfluoroalkyl acids in serum of Korean children: occurrences, related sources, and associated health outcomes. *Sci Total Environ.* 645:958–65. <https://doi.org/10.1016/j.scitotenv.2018.07.177> PMID:30032090
- Kang JS, Choi JS, Park JW (2016). Transcriptional changes in steroidogenesis by perfluoroalkyl acids (PFOA and PFOS) regulate the synthesis of sex hormones in H295R cells. *Chemosphere.* 155:436–43. <https://doi.org/10.1016/j.chemosphere.2016.04.070> PMID:27139122
- Kato S, Itoh S, Yuasa M, Baba T, Miyashita C, Sasaki S, et al. (2016). Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children’s Health. *Environ Health Prev Med.* 21(5):334–44. <https://doi.org/10.1007/s12199-016-0534-2> PMID:27137816
- Khalil N, Ebert JR, Honda M, Lee M, Nahhas RW, Koskela A, et al. (2018). Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8–12 year old children: a pilot study. *Environ Res.* 160:314–21. <https://doi.org/10.1016/j.envres.2017.10.014> PMID:29040951
- Kim DH, Kim UJ, Kim HY, Choi SD, Oh JE (2016c). Perfluoroalkyl substances in serum from South Korean infants with congenital hypothyroidism and healthy infants – its relationship with thyroid hormones. *Environ Res.* 147:399–404. <https://doi.org/10.1016/j.envres.2016.02.037> PMID:26950028
- Kim HY, Kim K-N, Shin CH, Lim Y-H, Kim JI, Kim B-N, et al. (2020). The relationship between perfluoroalkyl substances concentrations and thyroid function in early childhood: a prospective cohort study. *Thyroid.* 30(11):1556–65. <https://doi.org/10.1089/thy.2019.0436> PMID:32368952
- Kim S, Choi K, Ji K, Seo J, Kho Y, Park J, et al. (2011). Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. *Environ Sci Technol.* 45(17):7465–72. <https://doi.org/10.1021/es202408a> PMID:21805959

- Kjeldsen LS, Bonfeld-Jørgensen EC (2013). Perfluorinated compounds affect the function of sex hormone receptors. *Environ Sci Pollut Res Int.* 20(11):8031–44. <https://doi.org/10.1007/s11356-013-1753-3> PMID:23764977
- Knox SS, Jackson T, Javins B, Frisbee SJ, Shankar A, Ducatman AM (2011). Implications of early menopause in women exposed to perfluorocarbons. *J Clin Endocrinol Metab.* 96(6):1747–53. <https://doi.org/10.1210/jc.2010-2401> PMID:21411548
- Kobayashi S, Sata F, Goudarzi H, Araki A, Miyashita C, Sasaki S, et al. (2021a). Associations among perfluorooctanesulfonic/perfluorooctanoic acid levels, nuclear receptor gene polymorphisms, and lipid levels in pregnant women in the Hokkaido study. *Sci Rep.* 11(1):9994. <https://doi.org/10.1038/s41598-021-89285-2> PMID:33976266
- Kobayashi S, Sata F, Ikeda-Araki A, Miyashita C, Itoh S, Goudarzi H, et al. (2021b). Associations among maternal perfluoroalkyl substance levels, fetal sex-hormone enzymatic gene polymorphisms, and fetal sex hormone levels in the Hokkaido study. *Reprod Toxicol.* 105:221–31. <https://doi.org/10.1016/j.reprotox.2021.09.003> PMID:34536543
- Kraugerud M, Zimmer KE, Ropstad E, Verhaegen S (2011). Perfluorinated compounds differentially affect steroidogenesis and viability in the human adrenocortical carcinoma (H295R) in vitro cell assay. *Toxicol Lett.* 205(1):62–8. <https://doi.org/10.1016/j.toxlet.2011.05.230> PMID:21641976
- Kristensen SL, Ramlau-Hansen CH, Ernst E, Olsen SF, Bonde JP, Vested A, et al. (2013). Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. *Hum Reprod.* 28(12):3337–48. <https://doi.org/10.1093/humrep/det382> PMID:24129614
- La Rocca C, Tait S, Guerranti C, Busani L, Ciardo F, Bergamasco B, et al. (2015). Exposure to endocrine disruptors and nuclear receptors gene expression in infertile and fertile men from Italian areas with different environmental features. *Int J Environ Res Public Health.* 12(10):12426–45. <https://doi.org/10.3390/ijerph121012426> PMID:26445054
- Lai KP, Lee JC, Wan HT, Li JW, Wong AY, Chan TF, et al. (2017a). Effects of in utero PFOS exposure on transcriptome, lipidome, and function of mouse testis. *Environ Sci Technol.* 51(15):8782–94. <https://doi.org/10.1021/acs.est.7b02102> PMID:28654245
- Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, et al. (2003). Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci.* 74(2):382–92. <https://doi.org/10.1093/toxsci/kfg122> PMID:12773772
- Lebeaux RM, Doherty BT, Gallagher LG, Zoeller RT, Hoofnagle AN, Calafat AM, et al. (2020). Maternal serum perfluoroalkyl substance mixtures and thyroid hormone concentrations in maternal and cord sera: the HOME Study. *Environ Res.* 185:109395. <https://doi.org/10.1016/j.envres.2020.109395> PMID:32222633
- Lee CK, Kang SG, Lee JT, Lee SW, Kim JH, Kim DH, et al. (2015b). Effects of perfluorooctane sulfuric acid on placental PRL-family hormone production and fetal growth retardation in mice. *Mol Cell Endocrinol.* 401:165–72. <https://doi.org/10.1016/j.mce.2014.10.026> PMID:25449418
- Lewis RC, Johns LE, Meeker JD (2015). Serum biomarkers of exposure to perfluoroalkyl substances in relation to serum testosterone and measures of thyroid function among adults and adolescents from NHANES 2011–2012. *Int J Environ Res Public Health.* 12(6):6098–114. <https://doi.org/10.3390/ijerph120606098> PMID:26035660
- Li L, Li X, Chen X, Chen Y, Liu J, Chen F, et al. (2018d). Perfluorooctane sulfonate impairs rat Leydig cell development during puberty. *Chemosphere.* 190:43–53. <https://doi.org/10.1016/j.chemosphere.2017.09.116> PMID:28985536
- Li C-H, Ren X-M, Guo L-H (2019b). Adipogenic activity of oligomeric hexafluoropropylene oxide (perfluorooctanoic acid alternative) through peroxisome proliferator-activated receptor  $\gamma$  pathway. *Environ Sci Technol.* 53(6):3287–95. <https://doi.org/10.1021/acs.est.8b06978> PMID:30785727

- Li C-H, Ren X-M, Ruan T, Cao L-Y, Xin Y, Guo L-H, et al. (2018b). Chlorinated polyfluorinated ether sulfonates exhibit higher activity toward peroxisome proliferator-activated receptors signalling pathways than perfluorooctanesulfonate. *Environ Sci Technol*. 52(5):3232–9. <https://doi.org/10.1021/acs.est.7b06327> PMID:29389105
- Li D, Zhang L, Zhang Y, Guan S, Gong X, Wang X (2019a). Maternal exposure to perfluorooctanoic acid (PFOA) causes liver toxicity through PPAR- $\alpha$  pathway and lowered histone acetylation in female offspring mice. *Environ Sci Pollut Res Int*. 26(18):18866–75. <https://doi.org/10.1007/s11356-019-05258-z> PMID:31062244
- Li J, Cao H, Feng H, Xue Q, Zhang A, Fu J (2020e). Evaluation of the estrogenic/antiestrogenic activities of perfluoroalkyl substances and their interactions with the human estrogen receptor by combining *in vitro* assays and *in silico* modeling. *Environ Sci Technol*. 54(22):14514–24. <https://doi.org/10.1021/acs.est.0c03468> PMID:33111528
- Li L, Xu ZS, Song GW (2009). Study on the Langmuir aggregation of fluorinated surfactants on protein. *J Fluor Chem*. 130(2):225–30. <https://doi.org/10.1016/j.jfluchem.2008.10.007>
- Li Q-Q, Liu J-J, Su F, Zhang Y-T, Wu L-Y, Chu C, et al. (2022d). Chlorinated polyfluorinated ether sulfonates and thyroid hormone levels in adults: isomers of C8 Health Project in China. *Environ Sci Technol*. 56(10):6152–61. <https://doi.org/10.1021/acs.est.1c03757> PMID:35380809
- Li X, Wang Z, Klaunig JE (2019c). The effects of perfluorooctanoate on high fat diet induced non-alcoholic fatty liver disease in mice. *Toxicology*. 416:1–14. <https://doi.org/10.1016/j.tox.2019.01.017> PMID:30711707
- Li Y, Cheng Y, Xie Z, Zeng F (2017c). Perfluorinated alkyl substances in serum of the southern Chinese general population and potential impact on thyroid hormones. *Sci Rep*. 7(1):43380. <https://doi.org/10.1038/srep43380> PMID:28240244
- Li L, Li X, Chen X, Chen Y, Liu J, Chen F, et al. (2018d). Perfluorooctane sulfonate impairs rat Leydig cell development during puberty. *Chemosphere*. 190:43–53. <https://doi.org/10.1016/j.chemosphere.2017.09.116> PMID:28985536
- Li Y, Ramdhan DH, Naito H, Yamagishi N, Ito Y, Hayashi Y, et al. (2011). Ammonium perfluorooctanoate may cause testosterone reduction by adversely affecting testis in relation to PPAR $\alpha$ . *Toxicol Lett*. 205(3):265–72. <https://doi.org/10.1016/j.toxlet.2011.06.015> PMID:21712084
- Li Y, Xu Y, Fletcher T, Scott K, Nielsen C, Pineda D, et al. (2021b). Associations between perfluoroalkyl substances and thyroid hormones after high exposure through drinking water. *Environ Res*. 194:110647. <https://doi.org/10.1016/j.envres.2020.110647> PMID:33358873
- Li Z, Lin Z, Ji S, Lai KP, Wan HT, Wong CKC, et al. (2022e). Perfluorooctanesulfonic acid exposure altered hypothalamic metabolism and disturbed male fecundity. *Sci Total Environ*. 844:156881. <https://doi.org/10.1016/j.scitotenv.2022.156881> PMID:35753445
- Liang H, Wang Z, Miao M, Tian Y, Zhou Y, Wen S, et al. (2020). Prenatal exposure to perfluoroalkyl substances and thyroid hormone concentrations in cord plasma in a Chinese birth cohort. *Environ Health*. 19(1):127. <https://doi.org/10.1186/s12940-020-00679-7> PMID:33243245
- Liao Y, Wang J, Huang QS, Fang C, Kiyama R, Shen H, et al. (2012). Evaluation of cellular response to perfluorooctane sulfonate in human umbilical vein endothelial cells. *Toxicol In Vitro*. 26(3):421–8. <https://doi.org/10.1016/j.tiv.2012.01.011> PMID:22269386
- Lin CY, Wen LL, Lin LY, Wen TW, Lien GW, Hsu SH, et al. (2013). The associations between serum perfluorinated chemicals and thyroid function in adolescents and young adults. *J Hazard Mater*. 244–245:637–44. <https://doi.org/10.1016/j.jhazmat.2012.10.049> PMID:23177245

- Liu H, Huang Y, Pan Y, Cheng R, Li X, Li Y, et al. (2023c). Associations between per and polyfluoroalkyl ether sulfonic acids and vitamin D biomarker levels in Chinese newborns. *Sci Total Environ.* 866:161410. <https://doi.org/10.1016/j.scitotenv.2023.161410> PMID:36621489
- Liu H, Pan Y, Jin S, Li Y, Zhao L, Sun X, et al. (2020b). Associations of per-/polyfluoroalkyl substances with glucocorticoids and progestogens in newborns. *Environ Int.* 140:105636. <https://doi.org/10.1016/j.envint.2020.105636> PMID:32474218
- Liu H, Pan Y, Jin S, Sun X, Jiang Y, Wang Y, et al. (2021). Associations between six common per- and polyfluoroalkyl substances and estrogens in neonates of China. *J Hazard Mater.* 407:124378. <https://doi.org/10.1016/j.jhazmat.2020.124378> PMID:33139105
- Liu M, Zhang G, Meng L, Han X, Li Y, Shi Y, et al. (2022b). Associations between novel and legacy per- and polyfluoroalkyl substances in human serum and thyroid cancer: a case and healthy population in Shandong Province, East China. *Environ Sci Technol.* 56(10):6144–51. <https://doi.org/10.1021/acs.est.1c02850> PMID:34618433
- López-Doval S, Salgado R, Fernández-Pérez B, Lafuente A (2015). Possible role of serotonin and neuropeptide Y on the disruption of the reproductive axis activity by perfluorooctane sulfonate. *Toxicol Lett.* 233(2):138–47. <https://doi.org/10.1016/j.toxlet.2015.01.012> PMID:25623392
- López-Doval S, Salgado R, Lafuente A (2016). The expression of several reproductive hormone receptors can be modified by perfluorooctane sulfonate (PFOS) in adult male rats. *Chemosphere.* 155:488–97. <https://doi.org/10.1016/j.chemosphere.2016.04.081> PMID:27151425
- López-Doval S, Salgado R, Pereiro N, Moyano R, Lafuente A (2014). Perfluorooctane sulfonate effects on the reproductive axis in adult male rats. *Environ Res.* 134:158–68. <https://doi.org/10.1016/j.envres.2014.07.006> PMID:25171141
- Lopez-Espinosa M-J, Mondal D, Armstrong B, Bloom MS, Fletcher T (2012). Thyroid function and perfluoroalkyl acids in children living near a chemical plant. *Environ Health Perspect.* 120(7):1036–41. <https://doi.org/10.1289/ehp.1104370> PMID:22453676
- Lopez-Espinosa M-J, Mondal D, Armstrong BG, Eskenazi B, Fletcher T (2016). Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 6–9 years of age: a cross-sectional analysis within the C8 Health Project. *Environ Health Perspect.* 124(8):1269–75. <https://doi.org/10.1289/ehp.1509869> PMID:26794451
- Louisse J, Fragki S, Rijkers D, Janssen A, van Dijk B, Leenders L, et al. (2023). Determination of in vitro hepatotoxic potencies of a series of perfluoroalkyl substances (PFASs) based on gene expression changes in HepaRG liver cells. *Arch Toxicol.* 97(4):1113–31. <https://doi.org/10.1007/s00204-023-03450-2> PMID:36864359
- Louisse J, Rijkers D, Stoopen G, Janssen A, Staats M, Hoogenboom R, et al. (2020). Perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) increase triglyceride levels and decrease cholesterologenic gene expression in human HepaRG liver cells. *Arch Toxicol.* 94(9):3137–55. <https://doi.org/10.1007/s00204-020-02808-0> PMID:32588087
- Loveless SE, Finlay C, Everds NE, Frame SR, Gillies PJ, O'Connor JC, et al. (2006). Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology.* 220(2–3):203–17. <https://doi.org/10.1016/j.tox.2006.01.003> PMID:16448737
- Luo K, Liu X, Nian M, Wang Y, Qiu J, Yu H, et al.; Shanghai Birth Cohort (2021). Environmental exposure to per- and polyfluoroalkyl substances mixture and male reproductive hormones. *Environ Int.* 152:106496. <https://doi.org/10.1016/j.envint.2021.106496> PMID:33744484

- Luo Z, Shi X, Hu Q, Zhao B, Huang M (2012). Structural evidence of perfluorooctane sulfonate transport by human serum albumin. *Chem Res Toxicol.* 25(5):990–2. <https://doi.org/10.1021/tx300112p> PMID:22482699
- Lv Z, Li G, Li Y, Ying C, Chen J, Chen T, et al. (2013). Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate. *Environ Toxicol.* 28(9):532–42. <https://doi.org/10.1002/tox.20747> PMID:23983163
- Maisonet M, Calafat AM, Marcus M, Jaakkola JJK, Lashen H (2015). Prenatal exposure to perfluoroalkyl acids and serum testosterone concentrations at 15 years of age in female ALSPAC study participants. *Environ Health Perspect.* 123(12):1325–30. <https://doi.org/10.1289/ehp.1408847> PMID:26034840
- Maloney EK, Waxman DJ (1999). *trans*-Activation of PPAR $\alpha$  and PPAR $\gamma$  by structurally diverse environmental chemicals. *Toxicol Appl Pharmacol.* 161(2):209–18. <https://doi.org/10.1006/taap.1999.8809> PMID:10581215
- Marques E, Pfohl M, Wei W, Tarantola G, Ford L, Amaeze O, et al. (2022). Replacement per- and polyfluoroalkyl substances (PFAS) are potent modulators of lipogenic and drug metabolizing gene expression signatures in primary human hepatocytes. *Toxicol Appl Pharmacol.* 442:115991. <https://doi.org/10.1016/j.taap.2022.115991> PMID:35337807
- Masi M, Maddalon A, Iulini M, Linciano P, Galbiati V, Marinovich M, et al. (2022). Effects of endocrine disrupting chemicals on the expression of RACK1 and LPS-induced THP-1 cell activation. *Toxicology.* 480:153321. <https://doi.org/10.1016/j.tox.2022.153321> PMID:36113621
- Maso L, Trande M, Liberi S, Moro G, Daems E, Linciano S, et al. (2021). Unveiling the binding mode of perfluorooctanoic acid to human serum albumin. *Protein Sci.* 30(4):830–41. <https://doi.org/10.1002/pro.4036> PMID:33550662
- Messina P, Prieto G, Dodero V, Ruso JM, Schulz P, Sarmiento F (2005). Ultraviolet-circular dichroism spectroscopy and potentiometric study of the interaction between human serum albumin and sodium perfluorooctanoate. *Biopolymers.* 79(6):300–9. <https://doi.org/10.1002/bip.20353> PMID:16113999
- Murase W, Kubota A, Ikeda-Araki A, Terasaki M, Nakagawa K, Shizu R, et al. (2023). Effects of perfluorooctanoic acid (PFOA) on gene expression profiles via nuclear receptors in HepaRG cells: comparative study with in vitro transactivation assays. *Toxicology.* 494:153577. <https://doi.org/10.1016/j.tox.2023.153577> PMID:37302725
- Nakagawa T, Ramdhan DH, Tanaka N, Naito H, Tamada H, Ito Y, et al. (2012). Modulation of ammonium perfluorooctanoate-induced hepatic damage by genetically different PPAR $\alpha$  in mice. *Arch Toxicol.* 86(1):63–74. <https://doi.org/10.1007/s00204-011-0704-3> PMID:21499893
- Nielsen G, Heiger-Bernays WJ, Schlezinger JJ, Webster TF (2022). Predicting the effects of per- and polyfluoroalkyl substance mixtures on peroxisome proliferator-activated receptor alpha activity in vitro. *Toxicology.* 465:153024. <https://doi.org/10.1016/j.tox.2021.153024> PMID:34743024
- Nishimura Y, Moriya K, Kobayashi S, Ikeda-Araki A, Sata F, Mitsui T, et al. (2022). Association of exposure to prenatal perfluoroalkyl substances and estrogen receptor 1 polymorphisms with the second to fourth digit ratio in school-aged children: the Hokkaido study. *Reprod Toxicol.* 109:10–8. <https://doi.org/10.1016/j.reprotox.2022.02.002> PMID:35217143
- Olsen GW, Burris JM, Burlew MM, Mandel JH (2003b). Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. *J Occup Environ Med.* 45(3):260–70. <https://doi.org/10.1097/01.jom.0000052958.59271.10> PMID:12661183
- Olsen GW, Zobel LR (2007). Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. *Int Arch Occup Environ Health.* 81(2):231–46. <https://doi.org/10.1007/s00420-007-0213-0> PMID:17605032

- Owumi SE, Akomolafe AP, Imosemi IO, Odunola OA, Oyelere AK (2021b). *N*-acetyl cysteine co-treatment abates perfluorooctanoic acid-induced reproductive toxicity in male rats. *Andrologia*. 53(5):e14037. <https://doi.org/10.1111/and.14037> PMID:33724529
- Pereiro N, Moyano R, Blanco A, Lafuente A (2014). Regulation of corticosterone secretion is modified by PFOS exposure at different levels of the hypothalamic–pituitary–adrenal axis in adult male rats. *Toxicol Lett*. 230(2):252–62. <https://doi.org/10.1016/j.toxlet.2014.01.003> PMID:24440345
- Perkins RG, Butenhoff JL, Kennedy GL Jr, Palazzolo MJ (2004). 13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. *Drug Chem Toxicol*. 27(4):361–78. <https://doi.org/10.1081/DCT-200039773> PMID:15573472
- Petersen KU, Hærving KK, Flachs EM, Bonde JP, Lindh C, Hougaard KS, et al. (2022). Per- and polyfluoroalkyl substances (PFAS) and male reproductive function in young adulthood; a cross-sectional study. *Environ Res*. 212(Pt A):113157. <https://doi.org/10.1016/j.envres.2022.113157> PMID:35318009
- Petersen MS, Halling J, Jørgensen N, Nielsen F, Grandjean P, Jensen TK, et al. (2018). Reproductive function in a population of young Faroese men with elevated exposure to polychlorinated biphenyls (PCBs) and perfluorinated alkylate substances (PFAS). *Int J Environ Res Public Health*. 15(9):1880. <https://doi.org/10.3390/ijerph15091880> PMID:30200252
- Pinney SM, Fassler CS, Windham GC, Herrick RL, Xie C, Kushi LH, et al. (2023). Exposure to perfluoroalkyl substances and associations with pubertal onset and serum reproductive hormones in a longitudinal study of young girls in Greater Cincinnati and the San Francisco Bay Area. *Environ Health Perspect*. 131(9):97009. <https://doi.org/10.1289/EHP11811> PMID:37751325
- Preston EV, Webster TF, Oken E, Claus Henn B, McClean MD, Rifas-Shiman SL, et al. (2018). Maternal plasma per- and polyfluoroalkyl substance concentrations in early pregnancy and maternal and neonatal thyroid function in a prospective birth cohort: Project Viva (USA). *Environ Health Perspect*. 126(2):027013. <https://doi.org/10.1289/EHP2534> PMID:29488882
- Qazi MR, Xia Z, Bogdanska J, Chang SC, Ehresman DJ, Butenhoff JL, et al. (2009). 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 (PPARalpha). *Toxicology*. 260(1–3):68–76. <https://doi.org/10.1016/j.tox.2009.03.009> PMID:19464571
- Qin H, Niu Y, Luan H, Li M, Zheng L, Pan Y, et al. (2022c). Effects of legacy and emerging per- and polyfluoroalkyl substances on PPAR $\alpha$ / $\beta$ / $\gamma$  regulation and osteogenic/adipogenic differentiation. *Environ Int*. 170:107584. <https://doi.org/10.1016/j.envint.2022.107584> PMID:36265359
- Qiu L, Wang H, Dong T, Huang J, Li T, Ren H, et al. (2021). Perfluorooctane sulfonate (PFOS) disrupts testosterone biosynthesis via CREB/CRTC2/StAR signalling pathway in Leydig cells. *Toxicology*. 449:152663. <https://doi.org/10.1016/j.tox.2020.152663> PMID:33359577
- Qiu Z, Qu K, Luan F, Liu Y, Zhu Y, Yuan Y, et al. (2020). Binding specificities of estrogen receptor with perfluorinated compounds: a cross species comparison. *Environ Int*. 134:105284. <https://doi.org/10.1016/j.envint.2019.105284> PMID:31707300
- Qu JH, Lu CC, Xu C, Chen G, Qiu LL, Jiang JK, et al. (2016). Perfluorooctane sulfonate-induced testicular toxicity and differential testicular expression of estrogen receptor in male mice. *Environ Toxicol Pharmacol*. 45:150–7. <https://doi.org/10.1016/j.etap.2016.05.025> PMID:27310206
- Raymer JH, Michael LC, Studabaker WB, Olsen GW, Sloan CS, Wilcosky T, et al. (2012). Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. *Reprod Toxicol*. 33(4):419–27. <https://doi.org/10.1016/j.reprotox.2011.05.024> PMID:21736937

- Reardon AJF, Khodayari Moez E, Dinu I, Goruk S, Field CJ, Kinniburgh DW, et al.; APRON Study (2019). Longitudinal analysis reveals early-pregnancy associations between perfluoroalkyl sulfonates and thyroid hormone status in a Canadian prospective birth cohort. *Environ Int.* 129:389–99. <https://doi.org/10.1016/j.envint.2019.04.023> PMID:31150980
- Remy S, Govarts E, Wens B, De Boever P, Den Hond E, Croes K, et al. (2016). Metabolic targets of endocrine disrupting chemicals assessed by cord blood transcriptome profiling. *Reprod Toxicol.* 65:307–20. <https://doi.org/10.1016/j.reprotox.2016.08.018> PMID:27589886
- Rivera-Núñez Z, Kinkade CW, Khoury L, Brunner J, Murphy H, Wang C, et al. (2023). Prenatal perfluoroalkyl substances exposure and maternal sex steroid hormones across pregnancy. *Environ Res.* 220:115233. <https://doi.org/10.1016/j.envres.2023.115233> PMID:36621543
- Rosen MB, Abbott BD, Wolf DC, Corton JC, Wood CR, Schmid JE, et al. (2008a). Gene profiling in the livers of wild-type and PPAR $\alpha$ -null mice exposed to perfluorooctanoic acid. *Toxicol Pathol.* 36(4):592–607. <https://doi.org/10.1177/0192623308318208> PMID:18467677
- Rosen MB, Das KP, Wood CR, Wolf CJ, Abbott BD, Lau C (2013). Evaluation of perfluoroalkyl acid activity using primary mouse and human hepatocytes. *Toxicology.* 308:129–37. <https://doi.org/10.1016/j.tox.2013.03.011> PMID:23567314
- Rosen MB, Schmid JR, Corton JC, Zehr RD, Das KP, Abbott BD, et al. (2010). Gene expression profiling in wild-type and PPAR $\alpha$ -null mice exposed to perfluorooctane sulfonate reveals PPAR $\alpha$ -independent effects. *PPAR Res.* 2010:794739. <https://doi.org/10.1155/2010/794739> PMID:20936131
- Rosen Vollmar AK, Lin EZ, Nason SL, Santiago K, Johnson CH, Ma X, et al. (2023). Per- and polyfluoroalkyl substances (PFAS) and thyroid hormone measurements in dried blood spots and neonatal characteristics: a pilot study. *J Expo Sci Environ Epidemiol.* 33(5):737–47. <https://doi.org/10.1038/s41370-023-00603-4> PMID:37730931
- Rosenmai AK, Ahrens L, le Godec T, Lundqvist J, Oskarsson A (2018). Relationship between peroxisome proliferator-activated receptor alpha activity and cellular concentration of 14 perfluoroalkyl substances in HepG2 cells. *J Appl Toxicol.* 38(2):219–26. <https://doi.org/10.1002/jat.3515> PMID:28857218
- Rosenmai AK, Nielsen FK, Pedersen M, Hadrup N, Trier X, Christensen JH, et al. (2013). Fluorochemicals used in food packaging inhibit male sex hormone synthesis. *Toxicol Appl Pharmacol.* 266(1):132–42. <https://doi.org/10.1016/j.taap.2012.10.022> PMID:23142464
- Rosenmai AK, Taxvig C, Svingen T, Trier X, van Vugt-Lussenburg BM, Pedersen M, et al. (2016). Fluorinated alkyl substances and technical mixtures used in food paper-packaging exhibit endocrine-related activity in vitro. *Andrology.* 4(4):662–72. <https://doi.org/10.1111/andr.12190> PMID:27152447
- Rowan-Carroll A, Reardon A, Leingartner K, Gagné R, Williams A, Meier MJ, et al. (2021). High-throughput transcriptomic analysis of human primary hepatocyte spheroids exposed to per- and polyfluoroalkyl substances (PFAS) as a platform for relative potency characterization. *Toxicol Sci.* 181(2):199–214. <https://doi.org/10.1093/toxsci/kfab039> PMID:33772556
- Sabín J, Prieto G, González-Pérez A, Ruso JM, Sarmiento F (2006). Effects of fluorinated and hydrogenated surfactants on human serum albumin at different pHs. *Biomacromolecules.* 7(1):176–82. <https://doi.org/10.1021/bm050549w> PMID:16398513
- Sakai G, Hirao-Suzuki M, Koga T, Kobayashi T, Kamishikiroy J, Tanaka M, et al. (2022). Perfluorooctanoic acid (PFOA) as a stimulator of estrogen receptor-negative breast cancer MDA-MB-231 cell aggressiveness: evidence for involvement of fatty acid 2-hydroxylase (FA2H) in the stimulated cell migration. *J Toxicol Sci.* 47(4):159–68. <https://doi.org/10.2131/jts.47.159> PMID:35370244



- Salgado R, Pereiro N, López-Doval S, Lafuente A (2015). Initial study on the possible mechanisms involved in the effects of high doses of perfluorooctane sulfonate (PFOS) on prolactin secretion. *Food Chem Toxicol.* 83:10–6. <https://doi.org/10.1016/j.fct.2015.05.013> PMID:26032630
- Sarzo B, Ballesteros V, Iñiguez C, Manzano-Salgado CB, Casas M, Llop S, et al. (2021). Maternal perfluoroalkyl substances, thyroid hormones, and *DIO* genes: a Spanish cross-sectional study. *Environ Sci Technol.* 55(16):11144–54. <https://doi.org/10.1021/acs.est.1c01452> PMID:34314170
- Scharmach E, Buhrke T, Lichtenstein D, Lampen A (2012). Perfluorooctanoic acid affects the activity of the hepatocyte nuclear factor 4 alpha (HNF4 $\alpha$ ). *Toxicol Lett.* 212(2):106–12. <https://doi.org/10.1016/j.toxlet.2012.05.007> PMID:22609092
- Schlezingner JJ, Puckett H, Oliver J, Nielsen G, Heiger-Bernays W, Webster TF (2020). Perfluorooctanoic acid activates multiple nuclear receptor pathways and skews expression of genes regulating cholesterol homeostasis in liver of humanized PPAR $\alpha$  mice fed an American diet. *Toxicol Appl Pharmacol.* 405:115204. <https://doi.org/10.1016/j.taap.2020.115204> PMID:32822737
- Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Eldridge SR, Elcombe CR, et al. (2003). Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology.* 183(1–3):117–31. [https://doi.org/10.1016/S0300-483X\(02\)00511-5](https://doi.org/10.1016/S0300-483X(02)00511-5) PMID:12504346
- Sheng N, Li J, Liu H, Zhang A, Dai J (2016). Interaction of perfluoroalkyl acids with human liver fatty acid-binding protein. *Arch Toxicol.* 90(1):217–27. <https://doi.org/10.1007/s00204-014-1391-7> PMID:25370009
- Shipley JM, Hurst CH, Tanaka SS, DeRoos FL, Butenhoff JL, Seacat AM, et al. (2004). *trans*-Activation of PPAR $\alpha$  and induction of PPAR $\alpha$  target genes by perfluorooctane-based chemicals. *Toxicol Sci.* 80(1):151–60. <https://doi.org/10.1093/toxsci/kfh130> PMID:15071170
- Shrestha S, Bloom MS, Yucel R, Seegal RF, Wu Q, Kannan K, et al. (2015). Perfluoroalkyl substances and thyroid function in older adults. *Environ Int.* 75:206–14. <https://doi.org/10.1016/j.envint.2014.11.018> PMID:25483837
- Song M, Kim Y-J, Park Y-K, Ryu J-C (2012). Changes in thyroid peroxidase activity in response to various chemicals. *J Environ Monit.* 14(8):2121–6. <https://doi.org/10.1039/c2em30106g> PMID:22699773
- Song P, Li D, Wang X, Zhong X (2018). Effects of perfluorooctanoic acid exposure during pregnancy on the reproduction and development of male offspring mice. *Andrologia.* 50(8):e13059. <https://doi.org/10.1111/and.13059> PMID:29862542
- Sonthithai P, Suriyo T, Thiantanawat A, Watcharasi P, Ruchirawat M, Satayavivad J (2016). Perfluorinated chemicals, PFOS and PFOA, enhance the estrogenic effects of 17 $\beta$ -estradiol in T47D human breast cancer cells. *J Appl Toxicol.* 36(6):790–801. <https://doi.org/10.1002/jat.3210> PMID:26234195
- Sprengel J, Behnisch PA, Besselink H, Brouwer A, Vetter W (2021). In vitro human cell-based TTR-TR $\beta$  CALUX assay indicates thyroid hormone transport disruption of short-chain, medium-chain, and long-chain chlorinated paraffins. *Arch Toxicol.* 95(4):1391–6. <https://doi.org/10.1007/s00204-021-02994-5> PMID:33555371
- Su S, Billy LJ, Chang S, Gonzalez FJ, Patterson AD, Peters JM (2022a). The role of mouse and human peroxisome proliferator-activated receptor- $\alpha$  in modulating the hepatic effects of perfluorooctane sulfonate in mice. *Toxicology.* 465:153056. <https://doi.org/10.1016/j.tox.2021.153056> PMID:34861291

- Su Y, Santucci-Pereira J, Dang NM, Kanefsky J, Rahulkannan V, Hillegass M, et al. (2022b). Effects of pubertal exposure to butyl benzyl phthalate, perfluorooctanoic acid, and zeranol on mammary gland development and tumorigenesis in rats. *Int J Mol Sci.* 23(3):1398. <https://doi.org/10.3390/ijms23031398> PMID:35163327
- Suh CH, Cho NK, Lee CK, Lee CH, Kim DH, Kim JH, et al. (2011). Perfluorooctanoic acid-induced inhibition of placental prolactin-family hormone and fetal growth retardation in mice. *Mol Cell Endocrinol.* 337(1–2):7–15. <https://doi.org/10.1016/j.mce.2011.01.009> PMID:21241770
- Sun S, Wang J, Lu Y, Dai J (2018). Corticosteroid-binding globulin, induced in testicular Leydig cells by perfluorooctanoic acid, promotes steroid hormone synthesis. *Arch Toxicol.* 92(6):2013–25. <https://doi.org/10.1007/s00204-018-2207-y> PMID:29721586
- Takacs ML, Abbott BD (2007). Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. *Toxicol Sci.* 95(1):108–17. <https://doi.org/10.1093/toxsci/kfl135> PMID:17047030
- Toft G, Jönsson BAG, Bonde JP, Nørgaard-Pedersen B, Hougaard DM, Cohen A, et al. (2016). Perfluorooctane sulfonate concentrations in amniotic fluid, biomarkers of fetal Leydig cell function, and cryptorchidism and hypospadias in Danish boys (1980–1996). *Environ Health Perspect.* 124(1):151–6. <https://doi.org/10.1289/ehp.1409288> PMID:26046833
- Tsai M-S, Lin C-Y, Lin C-C, Chen M-H, Hsu SHJ, Chien K-L, et al. (2015). Association between perfluoroalkyl substances and reproductive hormones in adolescents and young adults. *Int J Hyg Environ Health.* 218(5):437–43. <https://doi.org/10.1016/j.ijheh.2015.03.008> PMID:25921520
- Tucker DK, Macon MB, Strynar MJ, Dagnino S, Andersen E, Fenton SE (2015). The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. *Reprod Toxicol.* 54:26–36. <https://doi.org/10.1016/j.reprotox.2014.12.002> PMID:25499722
- Umar Ijaz M, Rauf A, Mustafa S, Ahmed H, Ashraf A, Al-Ghanim K, et al. (2022). Pachypodol attenuates perfluorooctane sulphonate-induced testicular damage by reducing oxidative stress. *Saudi J Biol Sci.* 29(3):1380–5. <https://doi.org/10.1016/j.sjbs.2021.12.012> PMID:35280584
- van den Dungen MW, Rijk JCW, Kampman E, Steegenga WT, Murk AJ (2015). Steroid hormone related effects of marine persistent organic pollutants in human H295R adrenocortical carcinoma cells. *Toxicol In Vitro.* 29(4):769–78. <https://doi.org/10.1016/j.tiv.2015.03.002> PMID:25765474
- van Gerwen M, Alpert N, Alsen M, Ziadkhanpour K, Taioli E, Genden E (2020). The impact of smoking on the association between perfluoroalkyl acids (PFAS) and thyroid hormones: a National Health and Nutrition Examination Survey analysis. *Toxics.* 8(4):116. <https://doi.org/10.3390/toxics8040116> PMID:33316920
- Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ (2006). 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 X receptor-beta, and retinoid X receptor-alpha. *Toxicol Sci.* 92(2):476–89. <https://doi.org/10.1093/toxsci/kfl014> PMID:16731579
- Vested A, Ramlau-Hansen CH, Olsen SF, Bonde JP, Kristensen SL, Halldorsson TI, et al. (2013). Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men. *Environ Health Perspect.* 121(4):453–8. <https://doi.org/10.1289/ehp.1205118> PMID:23360585
- Wan HT, Zhao YG, Leung PY, Wong CK (2014). Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. *PLoS One.* 9(1):e87137. <https://doi.org/10.1371/journal.pone.0087137> PMID:24498028

- Wan HT, Zhao YG, Wong MH, Lee KF, Yeung WS, Giesy JP, et al. (2011). Testicular signalling is the potential target of perfluorooctanesulfonate-mediated subfertility in male mice. *Biol Reprod.* 84(5):1016–23. <https://doi.org/10.1095/biolreprod.110.089219> PMID:21209418
- Wan Ibrahim WN, Tofighi R, Onishchenko N, Rebellato P, Bose R, Uhlén P, et al. (2013). Perfluorooctane sulfonate induces neuronal and oligodendrocytic differentiation in neural stem cells and alters the expression of PPAR $\gamma$  in vitro and in vivo. *Toxicol Appl Pharmacol.* 269(1):51–60. <https://doi.org/10.1016/j.taap.2013.03.003> PMID:23500012
- Wang C, Ruan T, Liu J, He B, Zhou Q, Jiang G (2015d). Perfluorooctyl iodide stimulates steroidogenesis in H295R cells via a cyclic adenosine monophosphate signalling pathway. *Chem Res Toxicol.* 28(5):848–54. <https://doi.org/10.1021/tx5004563> PMID:25871633
- Wang F, Liu W, Jin Y, Dai J, Zhao H, Xie Q, et al. (2011b). Interaction of PFOS and BDE-47 co-exposure on thyroid hormone levels and TH-related gene and protein expression in developing rat brains. *Toxicol Sci.* 121(2):279–91. <https://doi.org/10.1093/toxsci/kfr068> PMID:21436126
- Wang H, Du H, Yang J, Jiang H, O K, Xu L, et al. (2019). PFOS, PFOA, estrogen homeostasis, and birth size in Chinese infants. *Chemosphere.* 221:349–55. <https://doi.org/10.1016/j.chemosphere.2019.01.061> PMID:30641376
- Wang L, Wang Y, Liang Y, Li J, Liu Y, Zhang J, et al. (2014b). PFOS induced lipid metabolism disturbances in BALB/c mice through inhibition of low-density lipoproteins excretion. *Sci Rep.* 4(1):4582. <https://doi.org/10.1038/srep04582> PMID:24694979
- Wang X, Bai Y, Tang C, Cao X, Chang F, Chen L (2018b). Impact of perfluorooctane sulfonate on reproductive ability of female mice through suppression of estrogen receptor  $\alpha$ -activated kisspeptin neurons. *Toxicol Sci.* 165(2):475–86. <https://doi.org/10.1093/toxsci/kfy167> PMID:29939337
- Wang Y, Aimuzi R, Nian M, Zhang Y, Luo K, Zhang J (2021b). Perfluoroalkyl substances and sex hormones in postmenopausal women: NHANES 2013–2016. *Environ Int.* 149:106408. <https://doi.org/10.1016/j.envint.2021.106408> PMID:33548847
- Webster GM, Rauch SA, Marie NS, Mattman A, Lanphear BP, Venners SA (2016). Cross-sectional associations of serum perfluoroalkyl acids and thyroid hormones in US adults: variation according to TPOAb and iodine status (NHANES 2007–2008). *Environ Health Perspect.* 124(7):935–42. <https://doi.org/10.1289/ehp.1409589> PMID:26517287
- Webster GM, Venners SA, Mattman A, Martin JW (2014). Associations between perfluoroalkyl acids (PFASs) and maternal thyroid hormones in early pregnancy: a population-based cohort study. *Environ Res.* 133:338–47. <https://doi.org/10.1016/j.envres.2014.06.012> PMID:25019470
- Wen LL, Lin LY, Su TC, Chen PC, Lin CY (2013). Association between serum perfluorinated chemicals and thyroid function in US adults: the National Health and Nutrition Examination Survey 2007–2010. *J Clin Endocrinol Metab.* 98(9):E1456–64. <https://doi.org/10.1210/jc.2013-1282> PMID:23864701
- Wen X, Baker AA, Klaassen CD, Corton JC, Richardson JR, Aleksunes LM (2019). Hepatic carboxylesterases are differentially regulated in PPAR $\alpha$ -null mice treated with perfluorooctanoic acid. *Toxicology.* 416:15–22. <https://doi.org/10.1016/j.tox.2019.01.014> PMID:30685356
- Wilson J, Berntsen HF, Zimmer KE, Verhaegen S, Frizzell C, Ropstad E, et al. (2016). Do persistent organic pollutants interact with the stress response? Individual compounds, and their mixtures, interaction with the glucocorticoid receptor. *Toxicol Lett.* 241:121–32. <https://doi.org/10.1016/j.toxlet.2015.11.014> PMID:26599974
- Wolf CJ, Schmid JE, Lau C, Abbott BD (2012). Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ) by perfluoroalkyl acids (PFAAs): further investigation of C4–C12 compounds. *Reprod Toxicol.* 33(4):546–51. <https://doi.org/10.1016/j.reprotox.2011.09.009> PMID:22107727

- Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD (2008a). Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicol Sci.* 106(1):162–71. <https://doi.org/10.1093/toxsci/kfn166> PMID:18713766
- Wolf DC, Moore T, Abbott BD, Rosen MB, Das KP, Zehr RD, et al. (2008b). Comparative hepatic effects of perfluorooctanoic acid and WY14,643 in PPAR-alpha knockout and wild-type mice. *Toxicol Pathol.* 36(4):632–9. <https://doi.org/10.1177/0192623308318216> PMID:18467680
- Wu L-L, Gao H-W, Gao N-Y, Chen F-F, Chen L (2009). Interaction of perfluorooctanoic acid with human serum albumin. *BMC Struct Biol.* 9(1):31. <https://doi.org/10.1186/1472-6807-9-31> PMID:19442292
- Wu X, Liang M, Yang Z, Su M, Yang B (2017). Effect of acute exposure to PFOA on mouse liver cells in vivo and in vitro. *Environ Sci Pollut Res Int.* 24(31):24201–6. <https://doi.org/10.1007/s11356-017-0072-5> PMID:28887612
- Xiao C, Grandjean P, Valvi D, Nielsen F, Jensen TK, Weihe P, et al. (2020). Associations of exposure to perfluoroalkyl substances with thyroid hormone concentrations and birth size. *J Clin Endocrinol Metab.* 105(3):735–45. <https://doi.org/10.1210/clinem/dgz147> PMID:31665456
- Xie X, Weng X, Liu S, Chen J, Guo X, Gao X, et al. (2021). Perfluoroalkyl and polyfluoroalkyl substance exposure and association with sex hormone concentrations: results from the NHANES 2015–2016. *Environ Sci Eur.* 33(1):69. <https://doi.org/10.1186/s12302-021-00508-9> PMID:36061407
- Xu C, Jiang Z-Y, Liu Q, Liu H, Gu A (2017). Estrogen receptor beta mediates hepatotoxicity induced by perfluorooctane sulfonate in mouse. *Environ Sci Pollut Res Int.* 24(15):13414–23. <https://doi.org/10.1007/s11356-017-8943-3> PMID:28386898
- Xu J, Shimpi P, Armstrong L, Salter D, Slitt AL (2016). PFOS induces adipogenesis and glucose uptake in association with activation of Nrf2 signalling pathway. *Toxicol Appl Pharmacol.* 290:21–30. <https://doi.org/10.1016/j.taap.2015.11.002> PMID:26548598
- Yan S, Wang J, Dai J (2015b). Activation of sterol regulatory element-binding proteins in mice exposed to perfluorooctanoic acid for 28 days. *Arch Toxicol.* 89(9):1569–78. <https://doi.org/10.1007/s00204-014-1322-7> PMID:25092180
- Yang M, Lee Y, Gao L, Chiu K, Meling DD, Flaws JA, et al. (2022). Perfluorooctanoic acid disrupts ovarian steroidogenesis and folliculogenesis in adult mice. *Toxicol Sci.* 186(2):260–8. <https://doi.org/10.1093/toxsci/kfac005> PMID:35104888
- Yang Q, Wang W, Liu C, Wang Y, Sun K (2016). Effect of PFOS on glucocorticoid-induced changes in human decidual stromal cells in the first trimester of pregnancy. *Reprod Toxicol.* 63:142–50. <https://doi.org/10.1016/j.reprotox.2016.06.003> PMID:27288094
- Yang Q, Xie Y, Alexson SE, Nelson BD, DePierre JW (2002a). Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochem Pharmacol.* 63(10):1893–900. [https://doi.org/10.1016/S0006-2952\(02\)00923-1](https://doi.org/10.1016/S0006-2952(02)00923-1) PMID:12034374
- Yao PL, Ehresman DJ, Rae JM, Chang SC, Frame SR, Butenhoff JL, et al. (2014). Comparative in vivo and in vitro analysis of possible estrogenic effects of perfluorooctanoic acid. *Toxicology.* 326:62–73. <https://doi.org/10.1016/j.tox.2014.10.008> PMID:25456267
- Yao Q, Gao Y, Zhang Y, Qin K, Liew Z, Tian Y (2021). Associations of paternal and maternal per- and polyfluoroalkyl substances exposure with cord serum reproductive hormones, placental steroidogenic enzyme and birth weight. *Chemosphere.* 285:131521. <https://doi.org/10.1016/j.chemosphere.2021.131521> PMID:34273704

- Yao Q, Shi R, Wang C, Han W, Gao Y, Zhang Y, et al. (2019). Cord blood per- and polyfluoroalkyl substances, placental steroidogenic enzyme, and cord blood reproductive hormone. *Environ Int.* 129:573–82. <https://doi.org/10.1016/j.envint.2019.03.047> PMID:31174145
- Yu WG, Liu W, Jin YH (2009a). Effects of perfluorooctane sulfonate on rat thyroid hormone biosynthesis and metabolism. *Environ Toxicol Chem.* 28(5):990–6. <https://doi.org/10.1897/08-345.1> PMID:19045937
- Yu WG, Liu W, Jin YH, Liu XH, Wang FQ, Liu L, et al. (2009b). 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.* 43(21):8416–22. <https://doi.org/10.1021/es901602d> PMID:19924978
- Yu WG, Liu W, Liu L, Jin YH (2011). Perfluorooctane sulfonate increased hepatic expression of OAPT2 and MRP2 in rats. *Arch Toxicol.* 85(6):613–21. <https://doi.org/10.1007/s00204-010-0613-x> PMID:21046362
- Zhang L, Ren X-M, Wan B, Guo L-H (2014b). Structure-dependent binding and activation of perfluorinated compounds on human peroxisome proliferator-activated receptor  $\gamma$ . *Toxicol Appl Pharmacol.* 279(3):275–83. <https://doi.org/10.1016/j.taap.2014.06.020> PMID:24998974
- Zhang N, Wang WS, Li WJ, Liu C, Wang Y, Sun K (2015b). Reduction of progesterone, estradiol and hCG secretion by perfluorooctane sulfonate via induction of apoptosis in human placental syncytiotrophoblasts. *Placenta.* 36(5):575–80. <https://doi.org/10.1016/j.placenta.2015.02.008> PMID:25748801
- Zhang S, Tan R, Pan R, Xiong J, Tian Y, Wu J, et al. (2018). Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women. *J Clin Endocrinol Metab.* 103(7):2543–51. <https://doi.org/10.1210/jc.2017-02783> PMID:29986037
- Zhang T, Sun H, Lin Y, Qin X, Zhang Y, Geng X, et al. (2013a). Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer. *Environ Sci Technol.* 47(14):7974–81. <https://doi.org/10.1021/es400937y> PMID:23777259
- Zhang Y, Cao X, Chen L, Qin Y, Xu Y, Tian Y, et al. (2020b). Exposure of female mice to perfluorooctanoic acid suppresses hypothalamic kisspeptin-reproductive endocrine system through enhanced hepatic fibroblast growth factor 21 synthesis, leading to ovulation failure and prolonged dioestrus. *J Neuroendocrinol.* 32(5):e12848. <https://doi.org/10.1111/jne.12848> PMID:32307816
- Zhang YM, Dong XY, Fan LJ, Zhang ZL, Wang Q, Jiang N, et al. (2017b). Poly- and perfluorinated compounds activate human pregnane X receptor. *Toxicology.* 380:23–9. <https://doi.org/10.1016/j.tox.2017.01.012> PMID:28115241
- Zhao B, Li L, Liu J, Li H, Zhang C, Han P, et al. (2014). Exposure to perfluorooctane sulfonate in utero reduces testosterone production in rat fetal Leydig cells. *PLoS One.* 9(1):e78888. <https://doi.org/10.1371/journal.pone.0078888> PMID:24454680
- Zhao B, Lian Q, Chu Y, Hardy DO, Li XK, Ge RS (2011b). The inhibition of human and rat 11 $\beta$ -hydroxysteroid dehydrogenase 2 by perfluoroalkylated substances. *J Steroid Biochem Mol Biol.* 125(1–2):143–7. <https://doi.org/10.1016/j.jsbmb.2010.12.017> PMID:21237268
- Zhao C, Wang S, Zhai Y, Wang M, Tang Y, Li H, et al. (2023). Direct inhibition of human and rat 11 $\beta$ -hydroxysteroid dehydrogenase 2 by per- and polyfluoroalkyl substances: structure–activity relationship and in silico docking analysis. *Toxicology.* 488:153484. <https://doi.org/10.1016/j.tox.2023.153484> PMID:36878351

- Zhao Y, Tan YS, Haslam SZ, Yang C (2010). Perfluorooctanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57BL/6 mice. *Toxicol Sci.* 115(1):214–24. <https://doi.org/10.1093/toxsci/kfq030> PMID:20118188
- Zhong SQ, Chen ZX, Kong ML, Xie YQ, Zhou Y, Qin XD, et al. (2016). Testosterone-mediated endocrine function and TH1/TH2 cytokine balance after prenatal exposure to perfluorooctane sulfonate: by sex status. *Int J Mol Sci.* 17(9):1509. <https://doi.org/10.3390/ijms17091509> PMID:27626407
- Zhou Y, Hu L-W, Qian ZM, Chang J-J, King C, Paul G, et al. (2016). Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: by sex status. *Environ Int.* 94:189–95. <https://doi.org/10.1016/j.envint.2016.05.018> PMID:27258660
- Zhou Y, Hu L-W, Qian ZM, Geiger SD, Parrish KL, Dharmage SC, et al. (2017). Interaction effects of polyfluoroalkyl substances and sex steroid hormones on asthma among children. *Sci Rep.* 7(1):899. <https://doi.org/10.1038/s41598-017-01140-5> PMID:28420867