Experimental Data Reviewed for Notification Level (NL) Recommendations for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) in Drinking Water

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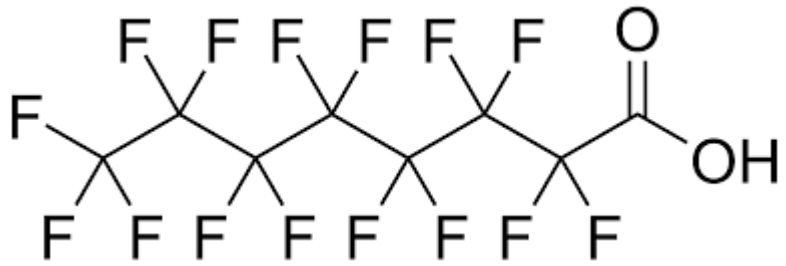
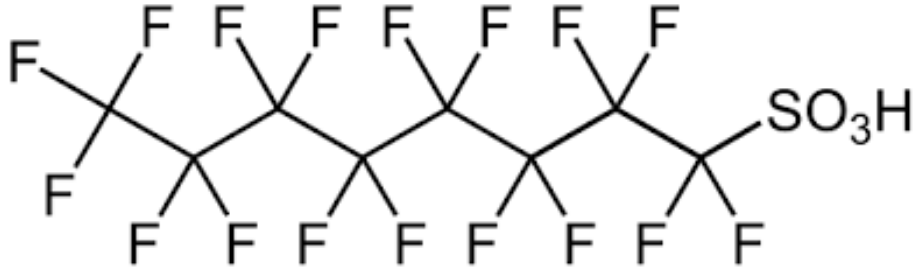
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

PFOA and PFOS

PFOA



PFOS



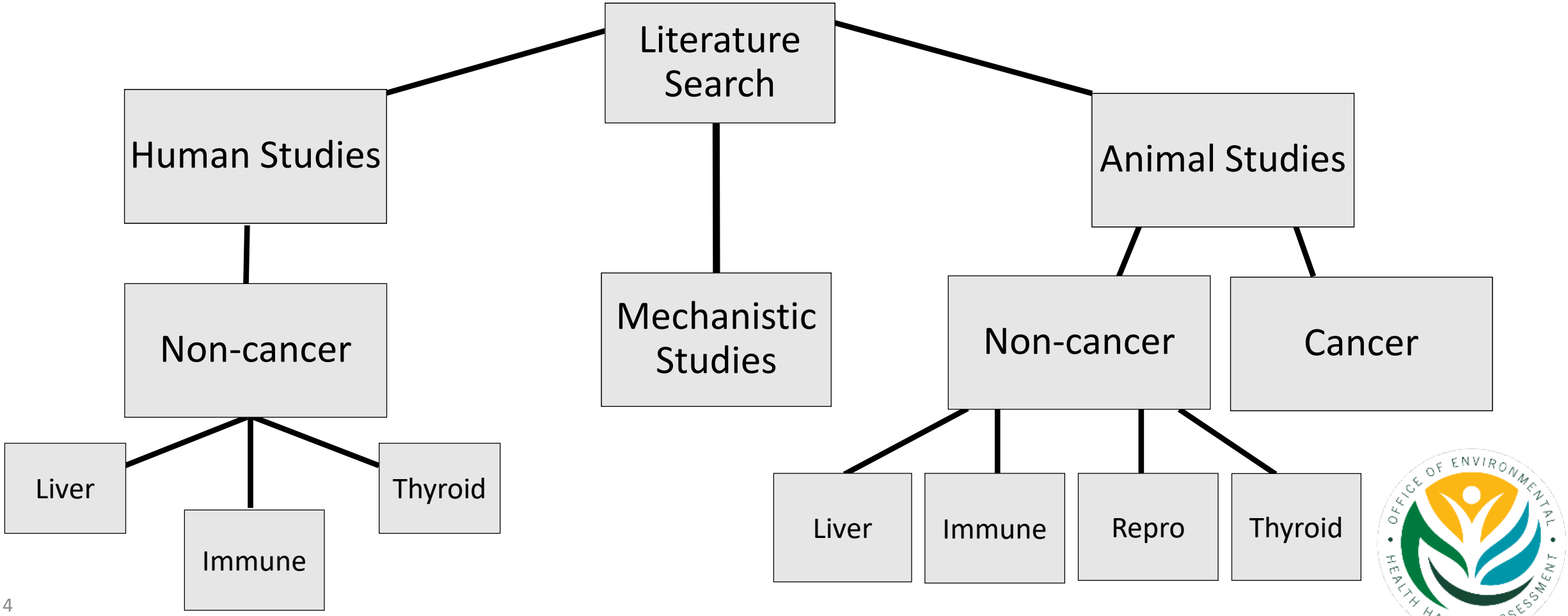
- Many industrial uses due to desirable chemical properties
- Very persistent in the environment and bioaccumulative
- The State's Biomonitoring California Program – detected in >98% of Californians tested

Sources of Data for Risk Assessments

- OEHHA reviewed available risk assessments for PFOA and PFOS for both toxicity evaluation and sources of toxicity studies
  - US EPA (2016)
  - State of New Jersey - Drinking Water Quality Institute (2017, 2018)
  - NTP Monograph (2016) – Immunotoxicity
  - ATSDR draft (2018)

- OEHHA did a literature search to identify studies published since 2016
- NTP 2018 chronic toxicity and cancer data

Data Reviewed for PFOA and PFOS Notification Level Recommendations



PFOA – Noncancer Effects

- Notification Level – animal toxicity studies since 2016
  - Liver toxicity – 16 studies
    - Increased liver weight, increased serum ALT and AST, hepatocyte hypertrophy, hepatocyte cytoplasmic alteration, necrosis, apoptosis, changes in lipid homeostasis, and other effects
  - Immunotoxicity – 7 studies
    - Decreased spleen and thymus weight, changes in cytokine levels, reduced antibody response, and other effects
  - Thyroid toxicity – 5 studies
    - Decreased thyroid weight, follicular cell hypertrophy, changes in thyroid hormone levels
  - Reproductive toxicity – 10 studies
    - Testicular and sperm effects in males, developmental effects, changes in sex hormones in both sexes, and other effects
    - PFOA listed for developmental toxicity under Proposition 65

- Candidate studies for the notification level were critically evaluated
- PHG - updated literature search and all relevant toxic effects will be assessed

PFOA – Critical Study for the Noncancer Reference Level

- Critical study – Li et al. (2017) hepatotoxicity study in mice
  - Male and female Balb/c mice (n=30/sex/dose) given 0, 0.05, 0.5 or 2.5 mg/kg-day via oral gavage for 28 days
  - Lowest observed adverse effect level (LOAEL) of 0.05 mg/kg-day for liver effects
    - Liver effects: changes in mitochondrial membrane potential, increased apoptosis, oxidative DNA damage, increased liver weight, hypertrophy, and lipid accumulation in the cytoplasm
- Serum concentration is the better dose metric for point of departure (POD) determination due to the major differences in PFOA's half-life between rodents and humans
  - The LOAEL corresponds to serum concentration of 0.97 mg/L PFOA in female mice

PFOA and PFOS half-lives differ between rodents and humans

PFOA and PFOS half-lives

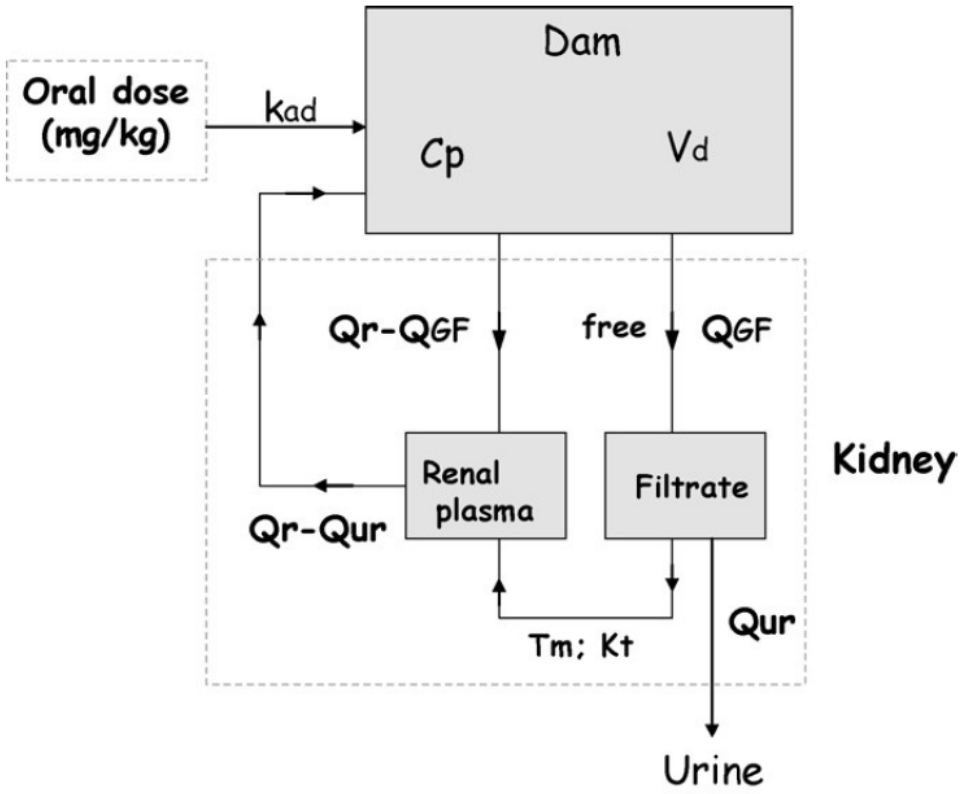
	Mouse	Rat	Human
PFOA	16 days (female) 22 days (male)	2-4 hours (female) 4-6 days (male)	2.3 years
PFOS	31-38 days (female) 36-43 days (male)	62-71 days (female) 38-41 days (male)	5.4 years

Source: US EPA

- For the same amount that humans consume compared to animals, higher serum concentrations would be observed in humans
- Kidney reabsorption is the main factor in toxicokinetics of PFOA and PFOS
- Studies that report serum concentrations generally do not need additional toxicokinetic adjustments

Physiologically-based pharmacokinetic (PBPK) models for PFOA and PFOS

Example: mouse PFOA model
Rodriguez et al . (2010)



Selected mouse PBPK models

Reference	Chemical	Model type, comment
Rodriguez et al. (2010)	PFOA	3-compartment, renal reabsorption
Wambaugh et al. (2013)	PFOA PFOS	3-compartment, renal reabsorption

Selected human PBPK models

Locissano et al. (2011)	PFOA PFOS	9-compartment, renal reabsorption
Convertino et al. (2018)	PFOA	2-compartment, rich dataset
Goeden et al. (2019)	PFOA	3-compartment, multi-generational

PBPK analysis

- Selected PBPK models were evaluated
- Due to availability of reported serum concentrations in the PFOA and PFOS animal critical studies, PBPK models were not used
- PFOA and PFOS toxicokinetics in humans were approximated with the clearance factor derived from the one-compartment PK model (US EPA approach)
- Further validation of rodent and human PBPK models

PFOA – Acceptable Daily Dose (ADD) for the Reference Level

- POD ÷ Uncertainty Factors = target human serum concentration
  - POD = 0.97 mg/L
  - UF = 300
    - √10 to account for differences between animals and humans, 10 for differences among people, √10 because the lowest dose had an adverse health effect, and √10 for database deficiency (reproductive toxicity)
    - no adjustment for a short duration study
  - target human serum concentration = 0.97 mg/L ÷ 300 = 3.2 µg/L

- ADD = target human serum concentration x clearance factor
  - Converts target human serum concentration to human equivalent dose (HED)
  - Clearance factor = 1.4×10^{-4} L/kg-day (US EPA, 2016)
  - ADD = 3.2 µg/L x (1.4×10^{-4} L/kg-day) = 0.45 ng/kg-day

PFOA Noncancer Reference Level (RL)

- RL = ADD x RSC ÷ DWI
  - RL = reference level
  - Acceptable daily dose (ADD) = 0.45 ng/kg-day
  - Relative source contribution (RSC) = 0.2
  - Drinking water intake (DWI) = 0.053 L/kg-day (OEHHA, 2012)

- RL = (0.45 ng/kg-day x 0.2) ÷ 0.053 L/kg-day = 2 ng/L or 2 parts per trillion (ppt)

PFOA and Cancer

Reference	Exposure	Liver (hepatocellular adenoma/carcinoma)	Pancreas (acinar cell adenoma/carcinoma)	Testis (Leydig cell adenoma)
Butenhoff et al. (2012)	Male rats - dietary for 106 weeks			✓
Biegel et al. (2001)	Male rats – dietary for 104 weeks	✓	✓	✓
Filgo et al. (2015)	Mice – in drinking water during pregnancy	✓		
NTP (2018)	Male rats – dietary for 107 weeks	✓	✓	

Liver and pancreatic tumor incidences in male rats exposed to PFOA in the diet for 107 weeks (NTP, 2018)

Conc (ppm)	Dose (mg/kg-d)	Plasma Conc (mg/L)	Human Equivalent Dose (mg/kg-d)	Hepatocellular (adenoma/ carcinoma[b])	Pancreatic acinar cell (adenoma/ carcinoma[b])
0	0	BD[a]	0	0/36	3/43
20	1.0	81.4	0.011	0/42	29/49***
40	2.3	131	0.018	7/35**	26/41***
80	4.8	160	0.022	11/37***	32/40***

a. Below limit of Detection
b. Incidence/effective number of animals

** p<0.01; ***p<0.001 pairwise comparison, Fisher's exact test

PFOA – Cancer Slope Factor

- Benchmark dose multisite tumor analysis using US EPA's Benchmark Dose Software – Benchmark response (BMR) of 5%
  - Human equivalent dose as the dose metric
  - Lower 95% confidence limit of the benchmark dose ($BMDL_{05}$) of 0.648 µg/kg-day

- Body weight (BW) scaling to determine human equivalent cancer potency
  - $BMDL_{05(human)} = BMDL_{05(animal)} \times (BW_{animal}/BW_{human})^{1/8}$
  - $BMDL_{05(human)} = 0.648$ µg/kg-day x 0.54 = 0.35 µg/kg-day

- Human cancer slope factor = BMR ÷ $BMDL_{05(human)}$
  - 0.05 ÷ 0.35 µg/kg-day = 0.143 $(\mu g/kg\text{-}day)^{-1}$ or 143 $(mg/kg\text{-}day)^{-1}$

PFOA – Cancer Reference Level

- RL = R ÷ (CSF X DWI)
  - RL = reference level
  - R = risk level of one in one million (10^{-6})
  - CSF = cancer slope factor of 143 $(mg/kg\text{-}day)^{-1}$
  - DWI = drinking water intake of 0.053 L/kg-day (OEHHA, 2012)

- RL = $10^{-6} \div (143\ (mg/kg\text{-}day)^{-1} \times 0.053\ L/kg\text{-}day) = 0.1$ ng/L or 0.1 ppt

- Age sensitivity factors were not included

PFOS – Noncancer Effects

- Notification Level – animal toxicity studies since 2016
  - Liver toxicity – 10 studies
    - Increased liver weight, increased serum ALT and AST, hepatocyte hypertrophy, hepatocyte cytoplasmic alteration, necrosis, apoptosis, changes in lipid homeostasis, and other effects
  - Immunotoxicity – 3 studies
    - Decreased thymus weight, decreased # of white blood cells, changes in cytokine levels, and other effects
  - Thyroid toxicity – 3 studies
    - Changes in thyroid hormone levels, decreased thyroid weight
  - Reproductive toxicity – 7 studies
    - Decreased testis weight, decreased sperm count, testicular damage, changes in hormone levels, and other effects
- PHG - updated literature search and all relevant toxic effects will be assessed

PFOS – Critical Study for the Noncancer Reference Level

- Critical study - Dong et al. (2009) immunotoxicity study
  - Adult male C57BL/6 mice (n=10) given 0, 0.008, 0.083, 0.417, 0.833, or 2.08 mg/kg-day via oral gavage for 28 days
  - NOAEL of 0.008 mg/kg-day for immune effects
    - Based on decreased plaque-forming cell response
    - Corresponds to serum concentration of 0.674 mg/L
- UF of 30 (3 for differences between animals and humans, 10 for differences among people), clearance factor of 8.1×10^{-5} L/kg-day (US EPA, 2016), drinking water intake rate of 0.053 L/kg-day, RSC of 0.2
- Noncancer reference level = 7 parts per trillion (ppt)

PFOS and Cancer

- Butenhoff et al. (2012) – PFOS in the diet for 2 years induced liver tumors in male and female rats
  - Male rats
    - significant increase in hepatocellular adenomas at the high dose ($p<0.05$)
    - Significant trend in pancreatic islet cell carcinomas ($p<0.05$)
  - Female rats
    - Significant increase in hepatocellular adenomas at the high dose ($p<0.05$)

- Highest dose in study ~ 1 mg/kg-day

PFOS – Cancer Reference Level

- "PFOS is being evaluated as a carcinogen because of the positive animal carcinogenicity bioassay data from Butenhoff et al. (2012), and because of the similarities in chemical structure and biologic activity between PFOS and PFOA."
  - Structure - linear 8-carbon perfluorinated molecules
  - Activity - similar noncancer toxicity endpoints observed for both PFOA and PFOS
    - Hepatotoxicity, immunotoxicity, reproductive toxicity, thyroid toxicity

- Human cancer slope factor = 45.5 $(mg/kg\text{-}day)^{-1}$ based on tumors in male rats

- Reference level of 0.4 ppt

Final Reference Levels for PFOA and PFOS

- Noncancer
  - 2 ppt for PFOA – based on liver toxicity in female mice (Li et al., 2017)
  - 7 ppt for PFOS – based on immunotoxicity in mice (Dong et al., 2009)
- Cancer
  - 0.1 ppt for PFOA – based on liver and pancreatic tumors in male rats (NTP, 2018)
  - 0.4 ppt for PFOS – based on liver tumors in rats (Butenhoff et al., 2012)

- Notification levels set at the "lowest levels that can be reliably detected in drinking water using currently available and appropriate technologies"
  - 5.1 ppt for PFOA and 6.5 ppt for PFOS

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