Summary of **Classical Toxicology** Studies of PFOA and PFOS

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1



Health Concerns with PFAS

- Extraordinarily persistent in the environment
- Widespread occurrence in water, air, soil, food
- Many PFAS bioaccumulate (readily absorbed but not easily eliminated)

2

- Health effects include liver toxicity, immunotoxicity, developmental toxicity, cancer, endocrine disruption
- PFAS can transfer to the fetus through the placenta and to the baby through breast milk.
- PFOS and PFOA were listed under Proposition 65 as developmental toxicants in November 2017



Epidemiology Literature PFOA/S

3

Epidemiology studies have been conducted in highly exposed workers, high exposure communities and the general population.

- high cholesterol AND elevations in liver enzymes in serum (indicating liver damage) associated with measured exposure to PFOA/S in all three types of studies.
- IARC: "There is limited evidence in humans for the carcinogenicity of perfluorooctanoic acid (PFOA). A positive association was observed for cancers of the testis and kidney."

Some support for an association between PFOA/S exposure and:

- ▶ incidence or prevalence of thyroid disease in women or children.
- chronic kidney disease (PFOS)
- ▶ low birth weight and SGA, and reproductive toxicity (PFOA/S).



NTP Systematic Review Immunotoxicity (2016)

- NTP conducted a systematic review to evaluate the evidence on exposure to PFOA or PFOS and immune-related health effects
- "NTP concludes that both PFOA and PFOS are presumed to be an immune hazard to humans based on a high level of evidence from animal studies that PFOA and PFOS suppressed the antibody response and a moderate level of evidence from studies in humans."

4

"The evidence that these chemicals affect multiple aspects of the immune system supports the overall conclusion that both PFOA and PFOS alter immune functions in humans."



Other PFAS Animal Toxicity

Animal testing is more limited for other long chains but effects seen in animal studies include toxicity to:

- Liver, reproductive system, immune system, thyroid, neurological system, kidney and heart, and impacts on lipid profiles
- Long half-lives in humans

Animal testing also limited for short chain PFAS, but USEPA has draft RfD for PFBS (less toxic than PFOA/S) and GenX (hexafluoropropylene oxide dimer) (on the same order of toxicity as PFOA/S)



Estimated Half-Lives of PFAS Across Species 6

	PFOA	PFOS	PFHxS	PFHxA
Rat	hours - days	weeks - months	days	hours
Mouse	weeks	weeks - months	weeks	hours
Monkey	weeks	months	months	hours
Human	2-3.5 yrs	3.4-5 yr	5.3-8.5 yrs	32 days

- Large differences across animal species
- Large differences across PFAS
- Differences between males and females
- Must account for this in reference exposure levels and read-across







Final Reference Levels for PFOA and PFOS

7

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

PFOA and Cancer

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



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	Pancreatic acinar cell adenoma/ carcinoma
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
** p<0.01; ***p<0.001 pairwise comparison, Fisher's exact test

- Data peer-reviewed by Pathology Working Group
- Plasma/serum concentration is the most appropriate dose metric for extrapolating toxicity data from rodent studies to humans

9

 Large difference in chemical half-life between rodents (1-3 weeks) and humans (2-3 years)



PFOS and Cancer

Butenhoff et al. (2012) – Hepatocellular adenoma in male rats and hepatocellular adenoma/carcinoma in female rats; also a significant trend in pancreatic islet cell carcinomas in male rats

- Oral in diet for 2 years
- ▶ These data were the basis of the Reference Level for cancer for PFOS of 0.4 ppt.

"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



11

Questions?

