NTP
National Toxicology Program

NTP Studies of Per- and Poly-fluoroalkyl Substances: Understanding Human Translation

Chad R. Blystone, Ph.D.
Division of the NTP
National Institute of Environmental Health Sciences

Board of Scientific Counselors
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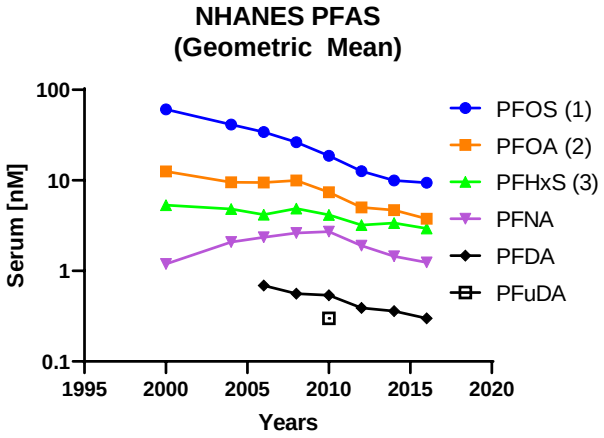
Poly- or Per-fluoroalkyl Substances (PFAS)

- PFAS are used in creating non-stick properties in a variety of products in addition to adding surfactant properties to products like fire fighting foams.
- Manufacturers agreed to discontinue use of PFOA and PFOS due to widespread exposure and health concerns.
- While exposure has declined for some PFAS, newer PFAS have been identified.



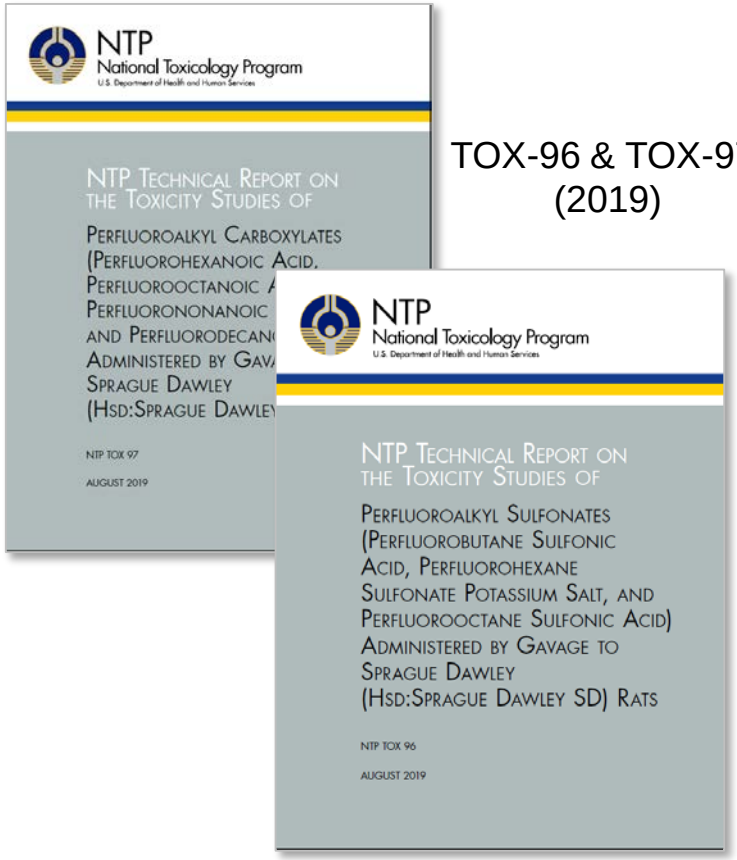
PFOA Cancer Assessments

- IARC (2016) classified PFOA as possibly carcinogenic in humans (Group 2B) based on *limited evidence* in humans and experimental animals

- US EPA (2016) concluded that there was *suggestive evidence* for carcinogenicity of PFOA in humans based on epidemiology and animal studies

NTP PFAS Program

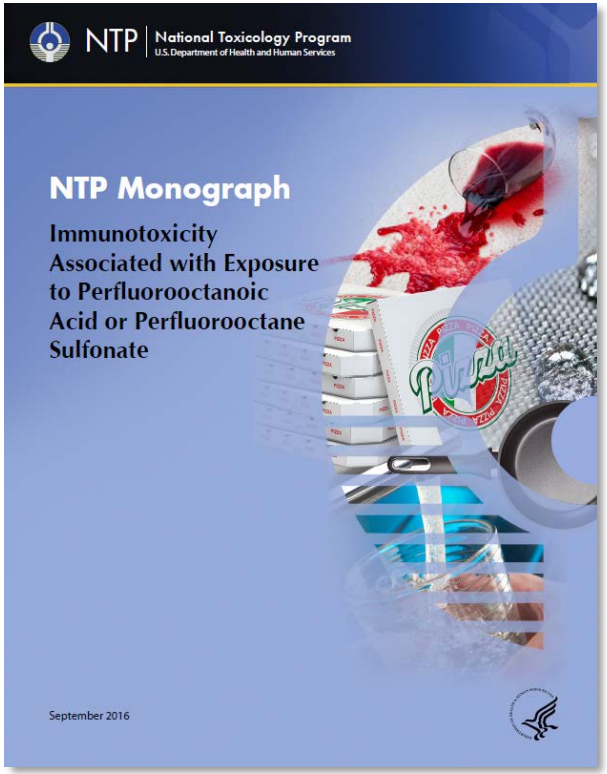
- Studies of PFAS conducted by the NTP include:
  - In vitro evaluations
  - Toxicokinetic, immunotoxicity, and 28-day toxicity studies of multiple PFAS in rodents
  - Carcinogenicity study of PFOA in rats



TOX-96 & TOX-97 (2019)

NTP PFAS Program

- NTP (2016) evaluation of human immunotoxicity hazard of PFOA and PFOS
  - PFOA and PFOS are *presumed immune hazards to humans*
- Newer PFAS evaluated under NTP's REACT program:
  - Coordinating with the US EPA
  - 75-100 chemicals under evaluation
  - In silico, in vitro, and short-term rodent evaluations of select endpoints



Characterization of Potential Human Health Impacts

- NTP generates data from in vitro or in vivo studies to inform public health on the potential toxicity of the substance tested.

- There are challenges of interpreting the direct human health impact of the findings from these studies.

- The recent peer-review of the Draft NTP Technical Report (TR) on the PFOA study of chronic toxicity and carcinogenicity is a recent example in considering the human health impact of the carcinogenicity findings.

NTP Technical Reports

Report Forward:

"The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection per se is not an indicator of a substance's carcinogenic potential."

PFOA Cancer Studies

- Ammonium perfluorooctanoate was evaluated in two chronic toxicity and carcinogenicity studies in rats, where exposure started in young adult animals.
  - Butenhoff et al., 2012: male and female rats exposed to 30 and 300 ppm in feed
  - Biegel et al., 2001: male rats exposed to 300 ppm in feed
- However, human exposure to PFOA occurs during early development.
  - Gestation and lactation periods of development = perinatal period
- Human health concern:
  - Does early perinatal exposure lead to changes in PFOA chronic toxicity and carcinogenicity response?

Study Hypothesis

- NTP tested the hypothesis that including perinatal exposure (gestation and lactation) would quantitively or qualitatively alter the PFOA response.

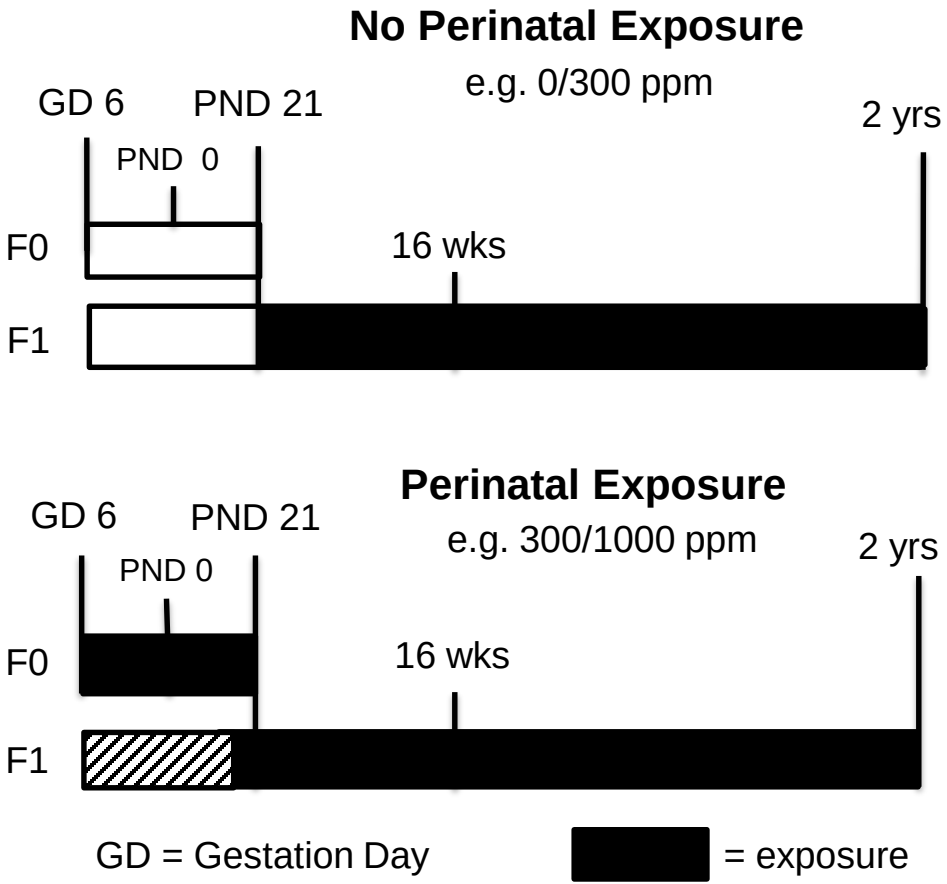
- Two types of comparisons were made during the analysis and interpretation of the data:

  1) Exposed groups were compared to the control group to determine if exposure increased effects in various endpoints.

  2) Exposed groups were also compared to determine if animals with perinatal exposure had different effects compared to animals without perinatal exposure.

Study Design

- Exposure started at post-natal day 21 (PND 21) in one cohort.
- In a second cohort, exposure started at gestational day (GD 6) and continued throughout postweaning until study termination.
- An interim necropsy at 16 weeks (19 weeks of age) occurred in both cohorts.



Male Pancreas Acinar Cell

Clear Evidence

Lesion	ppm	0	20	40	80
Acinus Hyperplasia	0	18/50 [2.7]^	32/50* [3.7]	37/50** [3.2]	31/50** [3.2]
Acinus Hyperplasia	300	23/50 [2.7]	27/50 [3.2]	38/50** [3.3]	33/50 [3.4]
Adenoma	0	3/50	28/50**	26/50**	32/50**
Adenoma	300	7/50	18/50**	30/50**	30/50**
Adenocarcinoma	0	0/50	3/50	1/50	3/50
Adenocarcinoma	300	0/50	2/50	1/50	3/50
Adenoma or Adenocarcinoma	0	3/50	29/50**	26/50**	32/50**
Adenoma or Adenocarcinoma	300	7/50	20/50**	30/50**	30/50**

Adenoma Historical Control: 45/340; 0/50 – 14/50
Adenocarcinoma Historical Control: 2/340; 0/50 – 1/50
Adenoma or Adenocarcinoma Historical Control: 145/340; 0/50 – 14/50
^ Average severity grade [1=minimal, 2=mild, 3=moderate, 4=marked]

* $p < 0.05$; ** $p < 0.01$ from control (0/0 ppm)
# $p < 0.05$ from non-perinatal exposure

Male Hepatocellular Neoplasms

Clear Evidence

Lesion	ppm	0	20	40	80
Adenoma	0	0/50	0/50	7/50*	11/50**
Adenoma	300	0/50	1/50	5/50	10/50**
Carcinoma	0	0	0	0	0
Carcinoma	300	0	0	0	4/50
Adenoma or Carcinoma	0	0/50	0/50	7/50*	11/50**
Adenoma or Carcinoma	300	0/50	1/50	5/50	12/50**

Adenoma Historical Control: 2/340; 0/50 – 1/50
Carcinoma Historical Control: 0/340
Adenoma or Carcinoma Historical Control: 2/340; 0/50 – 1/50

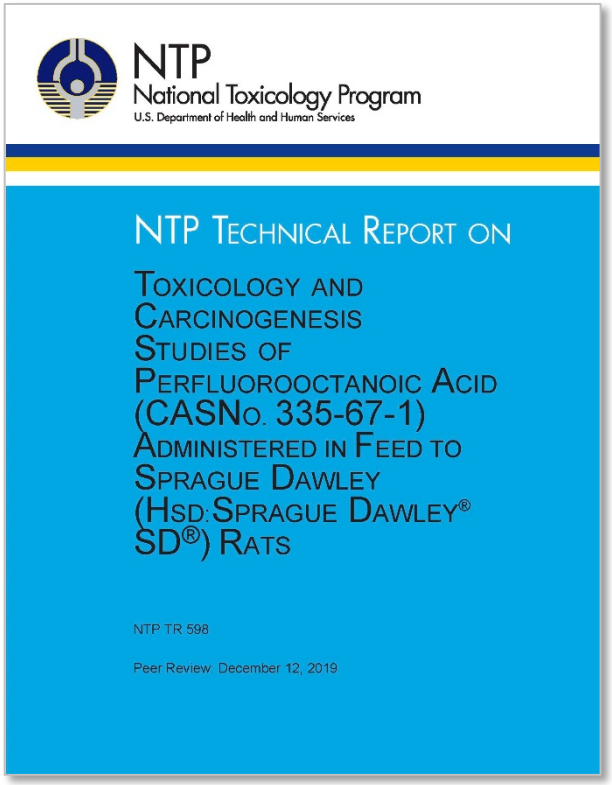
* $p < 0.05$; ** $p < 0.01$ from control (0/0 ppm)
# $p < 0.05$ from non-perinatal exposure

Similar lesions in the liver (necrosis, hepatocyte cytoplasmic alteration, hypertrophy, single cell death, pigment) as observed in 16-week males/females and 104-week females in addition to various foci.

Peer Review of PFOA Cancer Study

- PFOA draft TR was peer-reviewed by an external panel on December 12, 2019.

- Panel generally agreed with the conclusions, but was uncertain regarding the perinatal effect on hepatocellular carcinomas.



PFOA TR Conclusions

- Under the conditions of these 2-year feed studies, there was ***clear evidence of carcinogenic activity*** of PFOA in male Hsd:Sprague Dawley® SD® rats based on the increased incidence of **hepatocellular neoplasms** (predominately hepatocellular adenomas) and increased incidence of **acinar cell neoplasms** (predominately acinar cell adenomas) of the pancreas.

- The additional effect of perinatal exposure in combination with postweaning exposure was **uncertain and limited** to the observation of hepatocellular carcinomas.

- There was ***some evidence of carcinogenic activity*** of PFOA in female Hsd:Sprague Dawley® SD® rats based on the increased incidences of **pancreatic acinar cell adenoma or adenocarcinoma** (combined) neoplasms. The higher incidence of hepatocellular carcinomas and adenocarcinomas of the uterus may have been related to exposure.

- The combined perinatal and postweaning exposure **was not observed** to change the neoplastic or nonneoplastic response compared to the postweaning exposure alone in female rats.

NTP PFOA Cancer Study Health Impact

- The NTP study provided the most robust animal data on carcinogenic activity of PFOA to date:
  - Exposure was quantified in plasma at multiple time points
  - Lower exposure (20 ppm) and more exposure levels evaluated compared to previous studies, plus perinatal exposure included
  - Pancreatic neoplasms in male rats at all postweaning exposure levels (20, 40, 80 ppm) was a prominent finding
  - Response consistent with PPARα increased activity

Characterization of Potential Human Health Impacts

- Typically NTP Technical Reports will provide a general exposure comparison between animals and humans if exposure data are available.

- Previous assessments of carcinogenicity are included, whether animal studies, or hazard assessments by Federal or International Institutions.

- Generally NTP *does not* state that the findings from a study are *directly related or not related* to human health outcomes (per NTP TR Forward), but may identify consistencies in results or purported mechanisms with those in the literature.

BSC Questions

1) What should be NTP's responsibility for relating specific NTP study outcomes, using PFAS as an example, to potential human health impacts?

2) What can the NTP do to add value to the next phases of interpretation and application of data from NTP studies in the public health decision making processes?

Thank you

Questions?