

NTP Study of PFOA Chronic Toxicity and Carcinogenicity with and without Perinatal Exposure

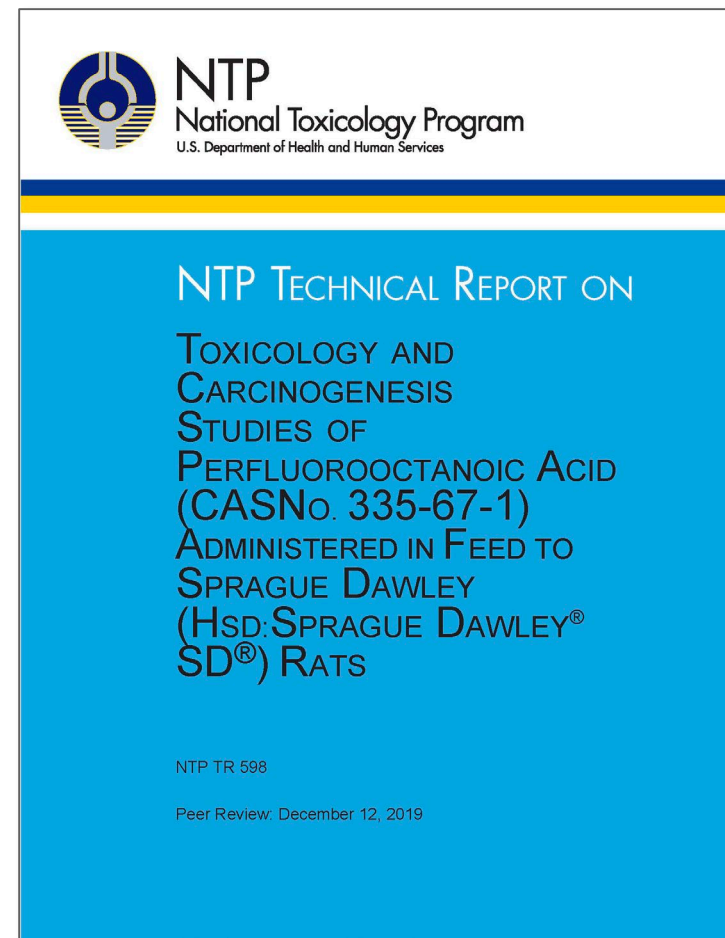
Experimental Design

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- National Toxicology Program (NTP) Draft Report on PFOA Chronic Toxicity and Carcinogenic Activity (TR-598):
 - NTP Technical Reports, which generally integrate multiple studies run under GLP requirements, provide description of methods, results, and NTP interpretation.
 - These reports undergo external peer review, which for the PFOA draft report has been scheduled for December 12th, 2019.
 - This presentation will provide an overview on the design and pathology peer review methods for this study.



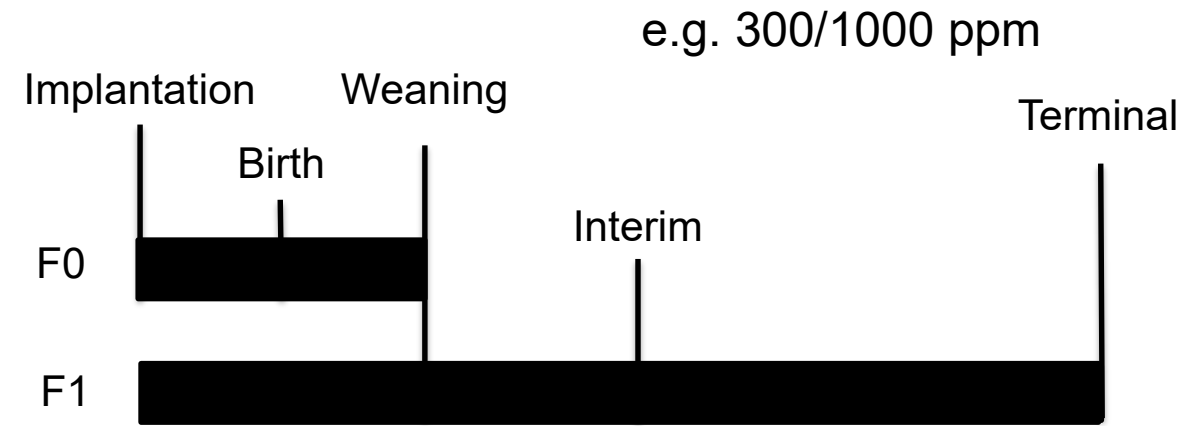
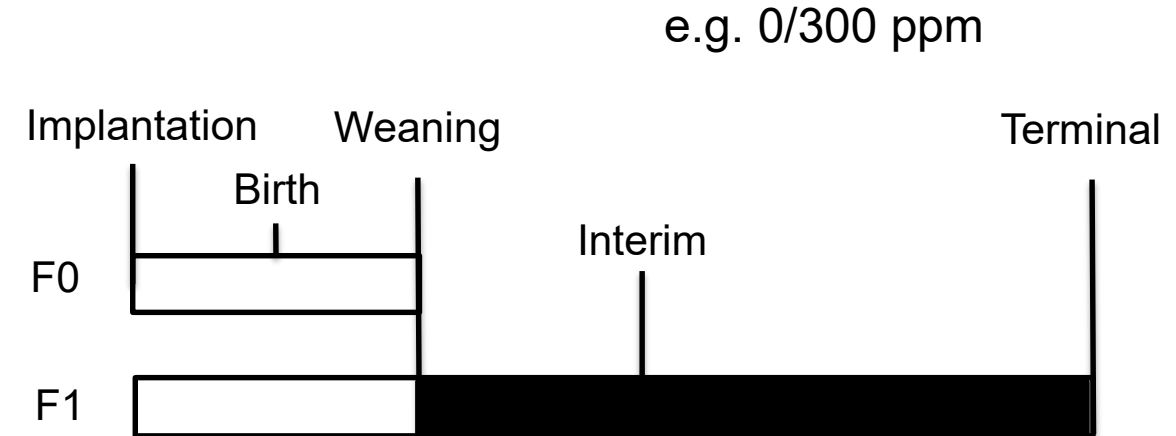



- PFOA chronic toxicity and carcinogenicity has been evaluated in two previous chronic studies (non-NTP studies), which exposure started in young adult animals (6-8 weeks old).
- PFOA exposure occurs throughout life, potentially impacting in utero development and early post-natal development.
- Due to concerns of lifetime exposure to PFOA, NTP tested the hypothesis that perinatal exposure (gestation and lactation) would quantitatively or qualitatively alter the response.



Exposure

- Initial study design (Study 1) was based on previous studies by the NTP to assess early life exposure contribution.
- Due to observed toxicity in males during the interim necropsy, the male portion of the study was stopped and males were restarted (Study 2).
- Groups of male and female rats (n = 50/group) were exposed to PFOA in feed. Postweaning exposure differed between the sexes due to differences in elimination rates (female > male).



 = exposure



- Two types of comparisons were made during the analysis and interpretation of the data:
 - 1) Exposed groups were compared to the 0/0 ppm control group to determine if exposure increased effects by pairwise comparisons in various endpoints.
 - 2) Exposed groups were also compared to determine if animals with perinatal exposure (gestation and lactation) had increased effects compared to animals without perinatal exposure.



Study 1 Comparisons (Male and Female)

		Post-weaning exposure			
ppm		0	150	300	1000
Perinatal exposure	0	M/F	M	M/F	F
	150	-	M	F	-
	300	-	-	M	F

- Two perinatal exposure levels (150 or 300 ppm)
- Postweaning exposure females higher (300 or 1000 ppm) than males (150 or 300 ppm) due to faster kinetics
- Overt toxicity observed in males so study ended at 21 weeks (so only have 16 week interim data)



Second study evaluated males only

Post-weaning exposure

Perinatal exposure

ppm	0	20	40	80
0	M	M	M	M
300	M	M	M	M

- Single perinatal exposure level (300 ppm)
- Lower exposure levels post-weaning (20, 40, 80 ppm)



- Perinatal evaluation (gestation through lactation)
 - Dam and pup body weights and littering parameters (e.g. litter size)
 - Dam and pup plasma PFOA concentrations and fetal concentrations were evaluated in the second study
- Interim evaluation at 16 weeks:
 - Body and organ weights
 - Histopathology and clinical chemistry
 - Plasma concentrations
 - Acyl-CoA oxidase and aromatase enzyme activity to assess potential mechanistic pathways
- Terminal evaluation at 104 weeks:
 - Histopathology