HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: PERFLUORONONANOIC ACID (PFNA)

New Jersey Drinking Water Quality Institute
Health Effects Subcommittee

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Background

- Drinking Water Quality Institute (DWQI)
  - Established by NJ SDWA (1984)
  - Charged with recommending Maximum Contaminant Levels (MCLs)
- Health Effects Subcommittee of DWQI is responsible for developing Health-based MCLs
  - Carcinogens: One in one million risk level from ***lifetime*** exposure (10^{-6})
  - Non-carcinogens: Not expected to result in “any adverse physiological effects from ingestion” for a ***lifetime***
- March 2014: DWQI requested to recommend MCL for perfluorononanoic acid (PFNA)

Perfluorinated Chemicals (PFCs)

- Perfluorinated chemicals (PFCs) are a class of manmade chemicals
  - Totally fluorinated carbon chains with charged functional group
  - Stable and resistant to chemical reactions
  - Water-soluble
- PFNA is a nine-carbon (C9) carboxylic acid
- PFOA (C8) and PFOS (C8-sulfonate) are more thoroughly characterized

PFNA Occurrence in Drinking Water

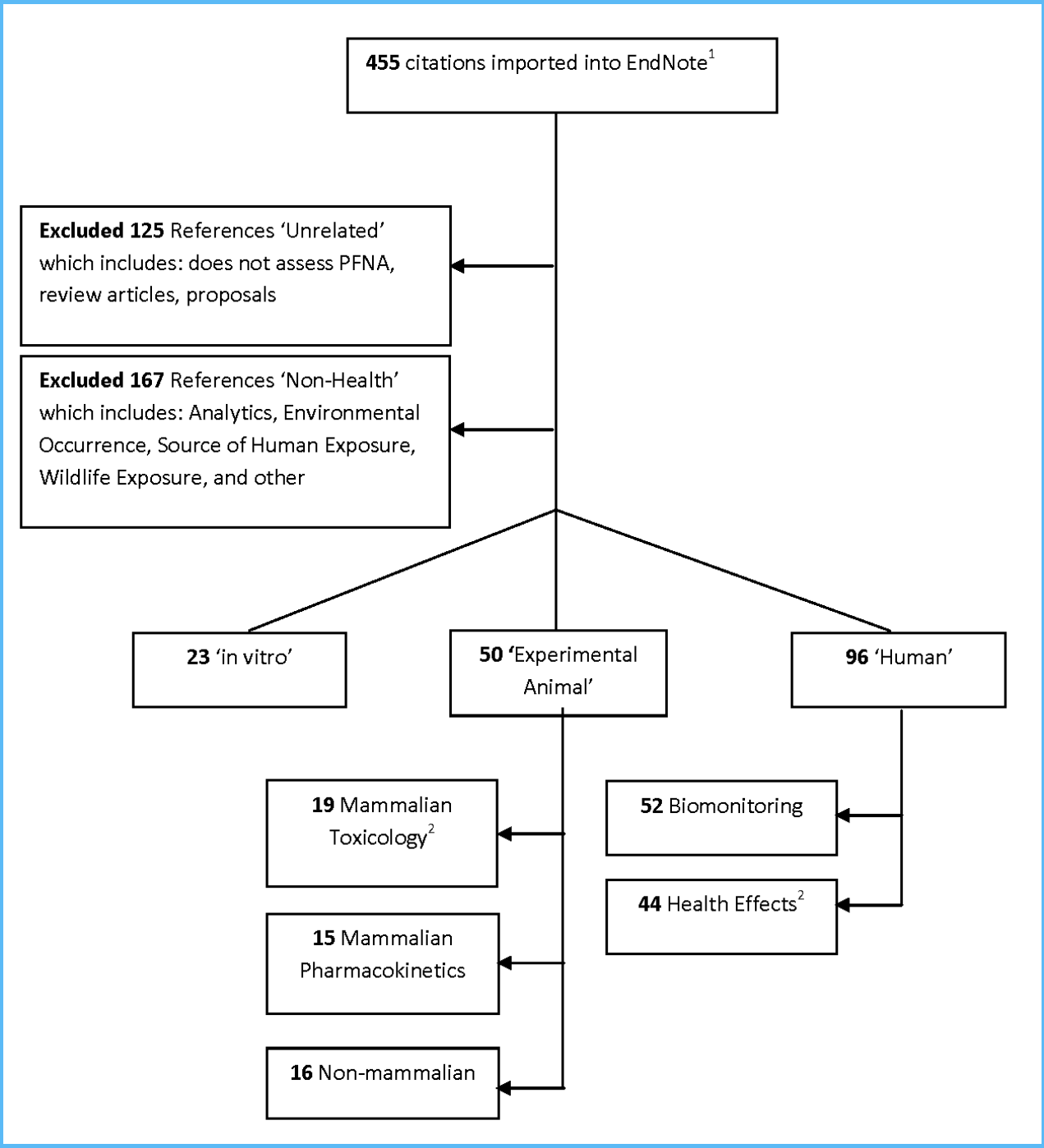
- UCMR3 as of January 2015:

New Jersey		National (excl. NJ)	
Number of PWS	% of PWS	Number of PWS	% of PWS
3/122	2.5%	7/3483	0.2%

- Paulsboro
  - 2009 NJDEP Occurrence Study: Raw-96 ng/L (ppt)
  - 2013 Follow-up: Raw-140 ng/L; Finished-150 ng/L
- Eight additional Gloucester County PWS up to 72 ng/L
- Gloucester County private wells up to 1,500 ng/L

Document Development

- Risk assessment process ***unchanged***
- New approach for presentation (pilot)
  - Documented literature search
  - Individual study tables
  - Summary tables for epidemiology and toxicology endpoints
- Request for additional technical information (May 2014) - submitted information was considered


455 citations imported into EndNote[1]
Excluded 125 References 'Unrelated' which includes: does not assess PFNA, review articles, proposals
Excluded 167 References 'Non-Health' which includes: Analytics, Environmental Occurrence, Source of Human Exposure, Wildlife Exposure, and other
23 'in vitro'
50 'Experimental Animal'
96 'Human'
19 Mammalian Toxicology[2]
15 Mammalian Pharmacokinetics
16 Non-mammalian
52 Biomonitoring
44 Health Effects[2]

European Chemical Agency (ECHA)

- Risk Assessment Committee – finalized classification of PFNA September 2014
  - Presumed to cause toxicity to unborn child
  - Suspected to affect fertility
  - Suspected human carcinogen
  - Causes toxicity to liver, thymus, and spleen
  - Causes harm to breast-fed child

Human Biomonitoring

- PFOA, PFOS, PFHxS, and PFNA are found in serum of 99% of the U.S. general population (NHANES)
- Found in human breast milk and human seminal fluid
- Medium/Mean/Geometric Mean of PFNA serum concentrations ranged from 0.3 to 2.4 ng/mL in general population human health studies

U.S. General Population Serum Levels

PFCs	Geometric Mean (95% CI) (ng/mL)		Selected Percentiles (ng/mL)			
			50th	75th	90th	95th
PFHxS	1.28	1.05-1.43	1.27	2.26	3.81	5.43
PFOS	6.31	1.04-6.84	6.51	10.48	15.62	21.68
PFOA	2.08	1.03-2.22	2.08	3.02	4.35	5.67
PFNA	0.88	0.81-0.97	0.86	1.30	1.95	2.54

[a] **CDC (2015)**

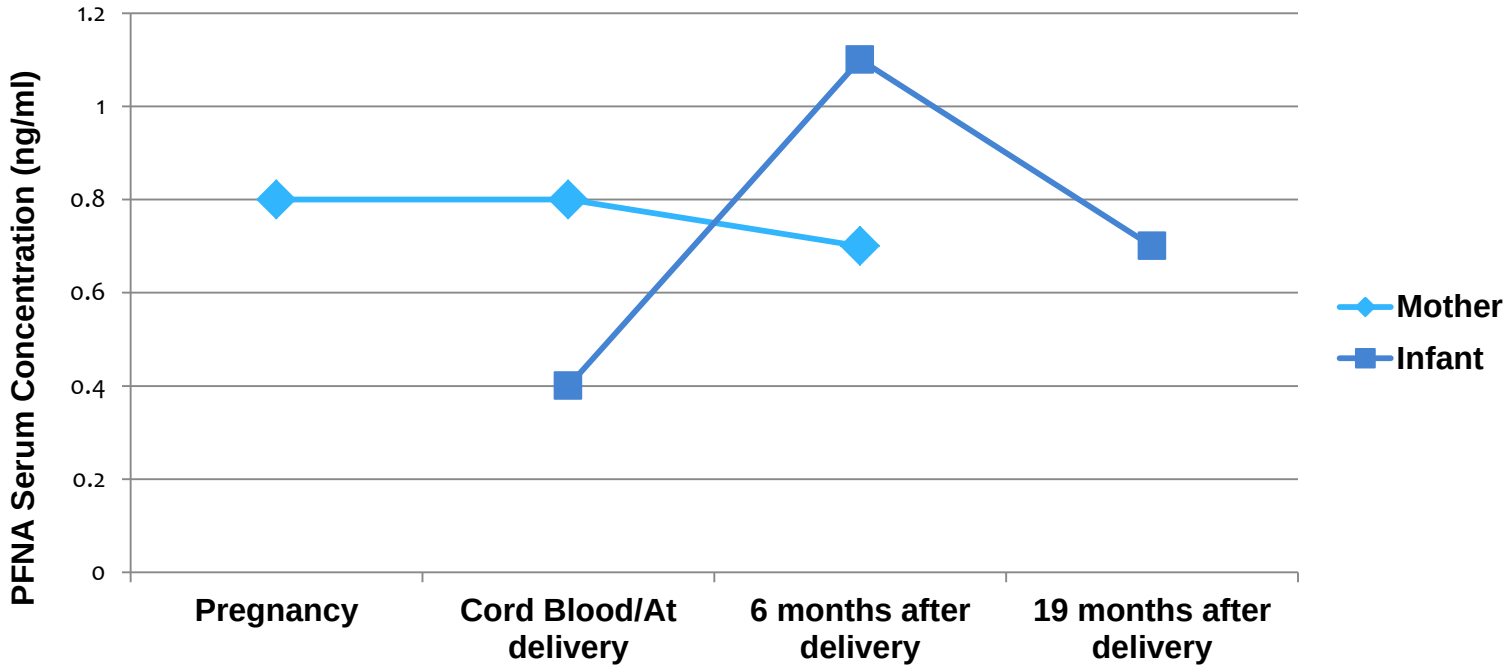
Unlikely that these U.S. general population PFNA serum concentrations are impacted by drinking water exposure

PFNA Toxicokinetics

- Non-reactive and not metabolized
- Primarily distributed to liver > serum > kidney
- Does not accumulate in fat
- Slowly excreted in humans, male and female mice, and male rats; rapidly excreted in female rats
- Excretion through urine and feces, menstruation, and breastfeeding in women
- Accumulates in the body over time; reaches steady state after prolonged exposure

Developmental Exposure

- Maternal – fetal transfer
- Infants consume more water per body weight
- Early life exposure via breast-feeding



*Data from Fromme et al., 2010

Half-lives

- Human estimates - decline in serum levels
  - PFNA: Not available
  - PFOA: Estimates of 2.3 - 8.9 years
- Human estimates - renal clearance
  - Support half-life ratio of PFNA: PFOA ≈ 2
- Rodent studies
  - Support half-life ratio of PFNA: PFOA $\geq$ 2

Human Studies

- 44 human epidemiology studies evaluated
- Endpoints include:
  - Serum lipids
  - Metabolic parameters
  - Immune system outcomes
  - Thyroid hormones and related outcomes
  - Reproductive outcomes
  - Birth outcomes
  - Neurobehavioral outcomes
  - Liver enzymes and bilirubin
  - Other outcomes
- Mostly cross-sectional studies – temporality cannot be established

Study Populations

- All but one study involved general population
  - Populations in the U.S., Asian nations, several European nations, and Canada
  - PFNA ranges ≈ 0.37-2.36 ng/mL
  - PFNA generally correlates with other PFCs in serum
- No studies of highly exposed communities
- One occupational study
  - Serum levels not reported

Associations

- Evidence strongest for serum cholesterol and the liver enzyme ALT
  - Consistent with most PFOA and PFOS studies
  - Primarily cross-sectional study design
- No evidence
  - Thyroid hormones
- Minimal evidence
  - Many endpoints are limited to one – few studies

Animal Toxicology Studies

- 10 short-term (14-day) oral studies:
  - 7 in male rats
  - 2 in male mice
  - 1 in male & female mice
- 4 oral reproductive/developmental studies:
  - 1 two-generation study in rats (Surflon S-111)
  - 3 gestational exposure
    - CD-1 mice
    - Wild-type and PPAR-alpha knockout (KO) mice
    - Rats
- 1 oral subchronic study (Surflon S-111) in rats
- 1 acute inhalation study in rats

Importance of PFNA Serum Levels in Toxicology Studies

- Half-life in humans (several years) vs. rodents (days to weeks)
- Human serum level > rodent serum level, from same external dose
- Quantitative human/rodent comparison based on serum levels (not external dose)
- Studies that do not provide serum levels contribute to hazard identification/qualitative evaluation

Toxicological Effects (PFNA and/or Surflon S-111)

- Profile of toxicity is generally similar to PFOA
  - PFNA is more persistent in the body
  - Causes generally similar effects at lower doses
- Toxicological effects include:
  - Weight loss
  - Liver – enlargement, microscopic changes (necrosis)
  - Kidney – enlargement, microscopic changes
  - Immune system (spleen & thymus) – atrophy and changes in immune cell populations
  - Testes – microscopic changes and other effects

Toxicological Effects (cont.)

- Pregnancy – decreased pregnancy rate, maternal weight loss, full litter resorptions
- Offspring – mortality, decreased weight gain persisting into adulthood, delays in reaching developmental milestones

- Some effects occur only after longer exposures to a given dose
- Chronic toxicity/carcinogenicity not studied

Mode of Action

- Generally not genotoxic
- PFNA activates receptors found in many tissues
  - These receptors are involved with carcinogenicity, liver toxicity, lipid metabolism, developmental toxicity, immune system toxicity, and other effects
- Specific toxicological mechanisms suggested for:
  - Effects on liver, immune system, male reproductive system, glucose and lipid metabolism, etc…
- Conclusion: Effects of PFNA in rodents are relevant to humans

Development of Health-Based MCL

- Weight of evidence for carcinogenicity
- Key and supporting studies/endpoints
- Point of Departure
- Uncertainty Factors
- Relative Source Contribution
- Serum: Drinking Water Ratio
- Development of health-based MCL

Weight of Evidence for Carcinogenicity

- No information on carcinogenicity
- Health-based MCL based on non-cancer effects

Critical Endpoint

- Increased maternal liver weight in pregnant mice
  - Serum levels and liver weights measured on GD 17 (one day after last dose)
  - Dose-related increase
    - LOAEL: 1 mg/kg/day
    - No NOAEL identified
  - Well-established toxicological effect of PFNA

Supporting Studies/Endpoints

- Other effects at similar or lower administered doses in same and/or other studies:
  - Liver necrosis (at doses lower than those causing increased liver weight)
  - Developmental toxicity including delayed growth persisting into adulthood
  - Immune system toxicity
  - Male reproductive system toxicity
  - Increased serum glucose levels

Point of Departure (POD)

- Benchmark dose modeling (BMD)
- Das et al., 2015
- 10% liver weight increase
- Lower 95% confidence limit (BMDL): **5,200 ng/ml**
- Similar BMDLs for other endpoints
  - Pup liver and body weight; developmental markers

Target Human Serum Level

- Analogous to Reference Dose on serum level basis
- Uncertainty Factors (UFs): **Total = 1,000**
  - 10 – Human variation
  - 3 – Animal-to-human extrapolation for toxicodynamic difference
  - 10 – Duration of exposure (shorter than chronic)
  - 3 – Incomplete database

$$\frac{5{,}200 \text{ ng/ml}}{1{,}000} = \textbf{5.2 ng/ml or 5,200 ng/L}$$

Relative Source Contribution (RSC)

- Accounts for non-drinking water sources
- Intended to prevent total exposure from exceeding the RfD
- Range of possible RSCs: 20% to 80%
  - Default RSC of 20% when insufficient chemical-specific information
  - Chemical-specific RSC if sufficient information
- Subtraction method – accounts for contribution of non-drinking water exposures to RfD (target human serum level)

RSC- “Subtraction Approach”

- PFNA serum levels from most recent NHANES
  - Geometric mean – 0.88 ng/ml
  - 95th percentile – 2.54 ng/ml
- Reflects U.S. background exposures due to food, air, dust, water, and consumer products
  - Unlikely to be influenced by drinking water exposures
- 95th percentile – protective of non-drinking water exposures

RSC Calculation

RSC =

$$\frac{\text{Target human serum level} - 95^{th}\ \text{NHANES serum level}}{\text{Target human serum level}} \times 100$$

$$\frac{5.2\ \text{ng/ml} - 2.54\ \text{ng/ml}}{5.2\ \text{ng/ml}} \times 100$$

RSC = 51.2 % ≈ **50.0% or 0.5**

Serum: Drinking Water Ratio

- Low levels in drinking water substantially increase total human exposure
- Mean PFOA serum:drinking water ratio – 100:1
- Half-life ratio of PFNA:PFOA ≈ 2
- Mean PFNA serum:drinking water ratio – 200:1
  - Represents a typical (not upper percentile) value
  - Not overly stringent

Health-Based MCL Recommendation

$$\frac{5200 \text{ ng/L} \times 0.5}{200 \text{ (ng/L)/(ng/L)}} = \boxed{\textbf{13 ng/L or 0.013 µg/L or 13 ppt}}$$

Where:

- Target Human Serum Level = 5.2 ng/mL or 5200 ng/L
- RSC= 50% or 0.5
- Serum: drinking water ratio = 200:1

  or 200 (ng/L) serum/(ng/L) drinking water

Uncertainties

- Ongoing exposure to 13 ppt → Estimated 4-fold increase in general population serum concentrations
- No epidemiology data from communities with drinking water exposure
- Toxicological endpoints that are potentially more sensitive not used as basis because serum PFNA data not available
- No chronic toxicology studies of cancer and other endpoints
- PFNA has not been studied for some low dose developmental effects caused by PFOA in animals
- 200:1 serum: drinking water ratio – considered reasonable estimate
- Potential for additive toxicity of PFCs not considered