HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: PERFLUOROOCTANE SULFONATE (PFOS)

New Jersey Drinking Water Quality Institute
Health Effects Subcommittee

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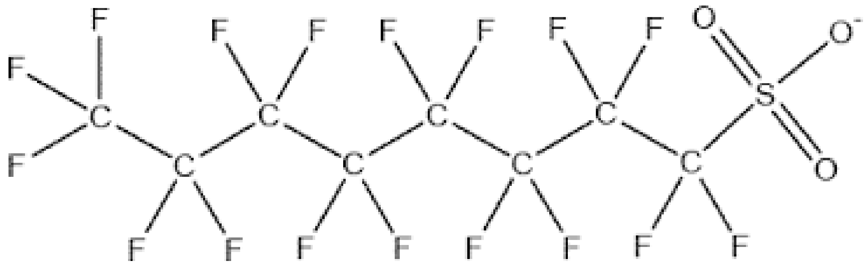
Background

- 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: NJDEP Commissioner requested DWQI recommend an MCL for perfluorooctane sulfonate (PFOS)

Perfluorinated Chemicals (PFCs)

- Perfluorinated chemicals (PFCs) are a class of human made chemicals
  - Part of larger group of highly fluorinated compounds: per- and polyfluoroalkyl substances (PFAS)
  - Totally fluorinated carbon chains with charged functional group
- PFOS is the eight-carbon sulfonate
- Extremely stable and resistant to chemical reactions
  - Persists indefinitely in the environment
- Water-soluble



Occurrence in NJ Public Water Systems

- UCMR3 Detections (All large [>10,000 users] and a few smaller PWS; finished water; Reporting Limit= 40 ng/L):
  - New Jersey PWS - 3.4%
  - United States PWS -1.9%

- NJDEP Database – Lower Reporting Limits, generally <5 ng/L
  - 76 PWS; raw or finished water, or individual wells or intakes; NJDEP studies & other NJDEP data - excludes UCMR3
  - Detected - 42% of PWS
  - >10 ng/L - 23% of PWS
  - Some PWS with detections have taken action (stopping use of contaminated wells, blending, or installing treatment)

Sources of Human Exposure

- Food and possibly house dust from non-specific sources such as consumer product use and breakdown
- Drinking water and house dust (in some cases) from point source emissions
  - Sources include industrial discharge; release of aqueous fire fighting foam in firefighting and training
- Recreationally caught **<u>fish</u>** may be an important source of PFOS exposure

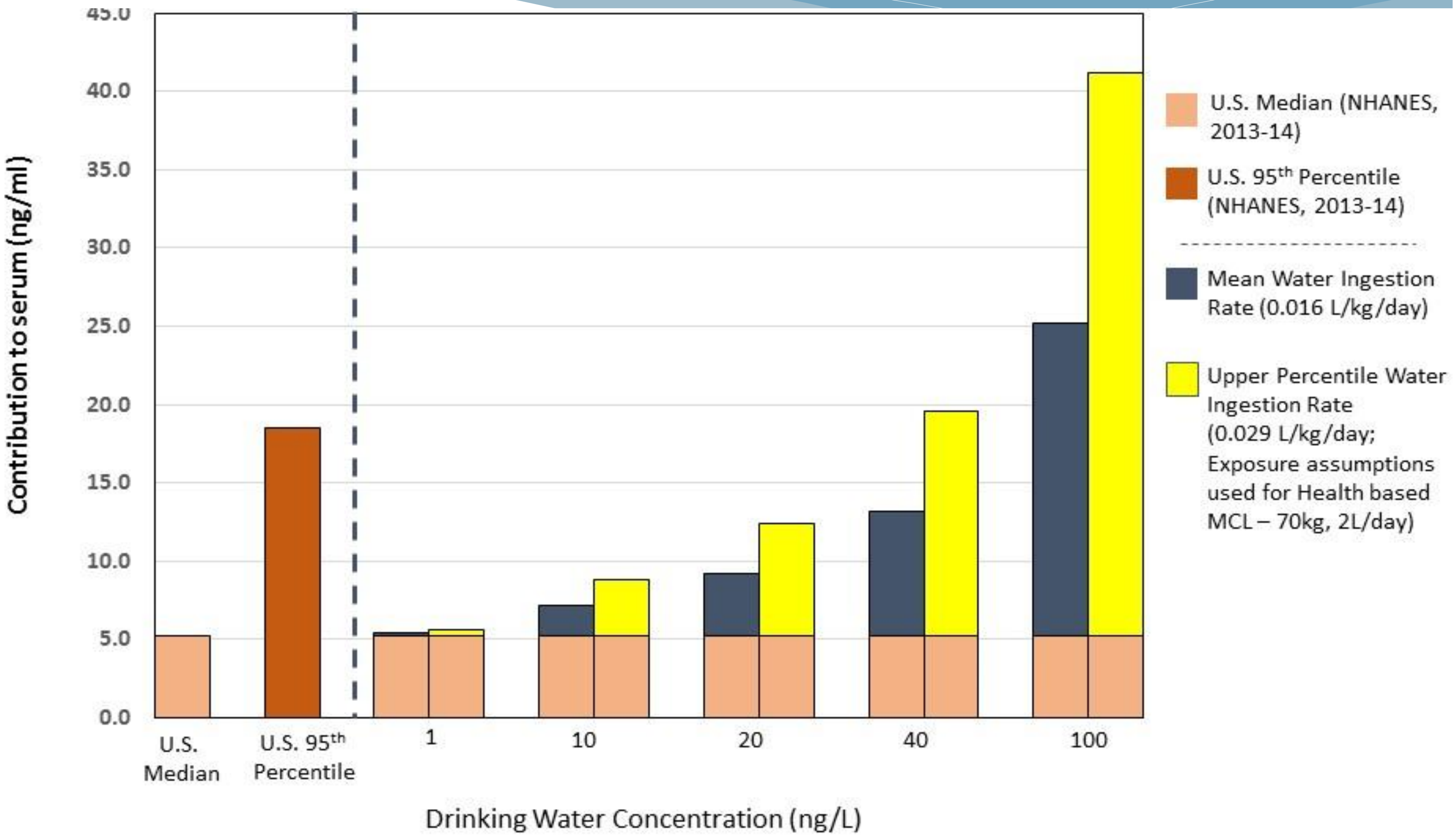
Human Biomonitoring

- PFOS is found in serum of 99% of the U.S. general population (NHANES)
  - Most recent (2013-14) data:
    - Median: 5.2 ng/ml
    - 95th percentile: 18.5 ng/ml
  - Levels decreasing over time (1999=30.4 ng/ml)
  - Primarily from non-drinking water sources including diet and consumer products
- Found in human cord blood serum, breast milk and seminal fluid

Toxicokinetics

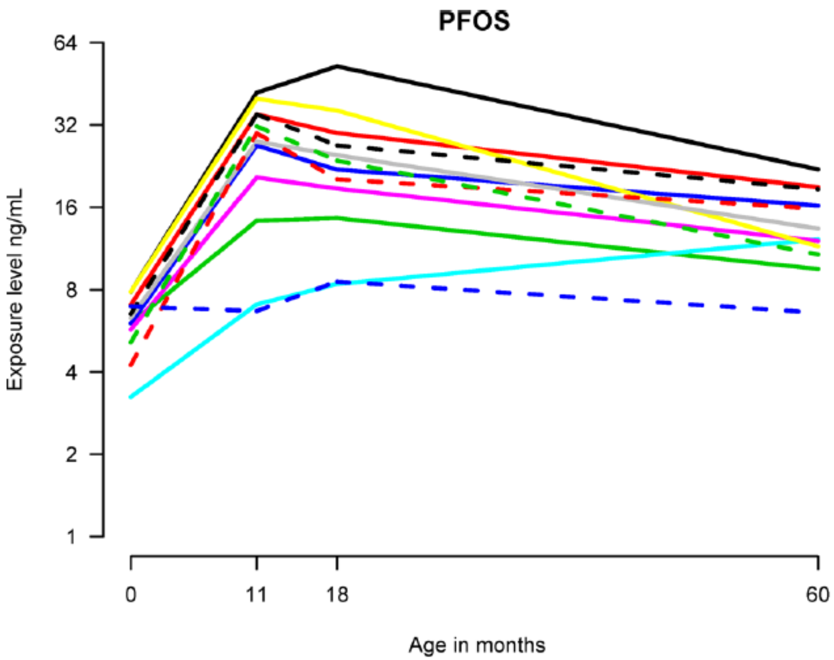
- Non-reactive and not metabolized
- Primarily distributed to liver > blood serum > kidney > lung > brain; does not accumulate in fat
- PFOS half-life estimates: about 5 years
  - Remains in body for many years after exposure ends
- Large variation in half-life among species
  - Higher serum level from same dose in humans v. animals.
  - Interspecies comparisons made on basis of internal dose
- Urine is major route of elimination; other routes: bile; menstruation and breastfeeding in women
- Accumulates in the body over time; reaches steady state after prolonged exposure
- Clearance factor: 8.1×10^{-5} L/kg/day relates external exposure to serum level.

Increases in Serum PFOS Concentrations Predicted from Ongoing Exposure to PFOS in Drinking Water



Developmental Exposure

- Serum levels in infants
  - At birth, similar to maternal serum levels
  - Increases during first few months of life
- Exposures in infants higher than in older individuals
  - From breastmilk or formula prepared with contaminated water
  - Consume more fluid per body weight
- Of concern because developmental effects and other effects from short term exposures are sensitive toxicological endpoints



Mogensen et al. 2015

Health Effects Subcommittee Document Development Process

- Comprehensive literature search
  - Approximately 2900 citations; 700 identified as potentially useful for assessment of health effects
- Detailed review:
  - Animal toxicology – 76 studies
  - Human epidemiology – 121 studies
- Individual and/or Summary tables for epidemiology and toxicology studies

Epidemiology - Study Populations

- Study populations include the U.S., Canada, and several European and Asian countries.
- General population (low-level exposures)
- Occupationally exposed workers
- No studies of communities with PFOS drinking water exposures

Associations with Health Effects

- Health effects investigated include:
  - Body weight, thyroid function, metabolic function, sex hormones, hepatic, immune, neurologic, and renal effects, serum lipids, non-lipid blood chemistry, and reproductive/developmental effects
- Strongest evidence
  - Decrease antibody response following vaccination
  - Increased serum uric acid/hyperuricemia
  - Increased total cholesterol

Epidemiology Conclusions

- Associations of PFOS with health endpoints
  - Such human data are not available for many other drinking water contaminants evaluated by DWQI
- Epidemiology findings are notable:
  - Consistency among results in different populations
  - Concordance with effects from animal toxicology studies, specifically for decreased immune response
  - Use of serum concentrations as measure of internal exposure
  - Associations within exposure range of the general population
  - Potential clinical importance
- Limitations preclude use of human data as quantitative basis for Health-based MCL:
  - But provides support for public health protective approach based on animal toxicology data

Toxicological Studies

- Numerous toxicological endpoints evaluated in rodents and non-human primates (monkeys)
- Notable toxicological effects include:
  - Hepatic:↑ liver weight and histopathological changes
  - Immune: ↓ immune response (i.e. plaque forming cell response), ↓ relative weight and cellularity of spleen and thymus, ↓ levels of immunoglobulins and cytokines, changes in immune cell populations
  - Serum lipids: ↓ cholesterol, HDL, LDL, triglycerides
  - Thyroid: Changes in thyroid hormone levels
  - Neurobehavioral: Changes in performance on behavioral tests
  - Reproductive/Developmental: ↑ neonatal mortality; ↓ body weight at birth and beyond; Hepatic, thyroid, metabolic, and immune effects from gestational exposure
  - Carcinogenicity: ↑ increased hepatic and thyroid tumors

Mode of Action

- Hepatic effects
  - Sometimes assumed to occur through peroxisome proliferator-activated receptor-alpha (PPARα)
    - Lower levels and/or intrinsic activity of hepatic PPAR-α in humans than in rodents
    - Relevance for human health risk assessment is subject to debate
  - However several lines of evidence suggest minor role, if any, for PPARα in hepatic effects of PFOS
    - PFOS is much less potent than known PPARα activators for *in vitro* binding to PPARα
    - PFOS caused liver weight increase and liver pathology in PPARα-null mice
    - In chronic two-year rat study, PFOS caused hepatocellular hypertrophy, necrosis, and liver tumors without evidence of peroxisome proliferation

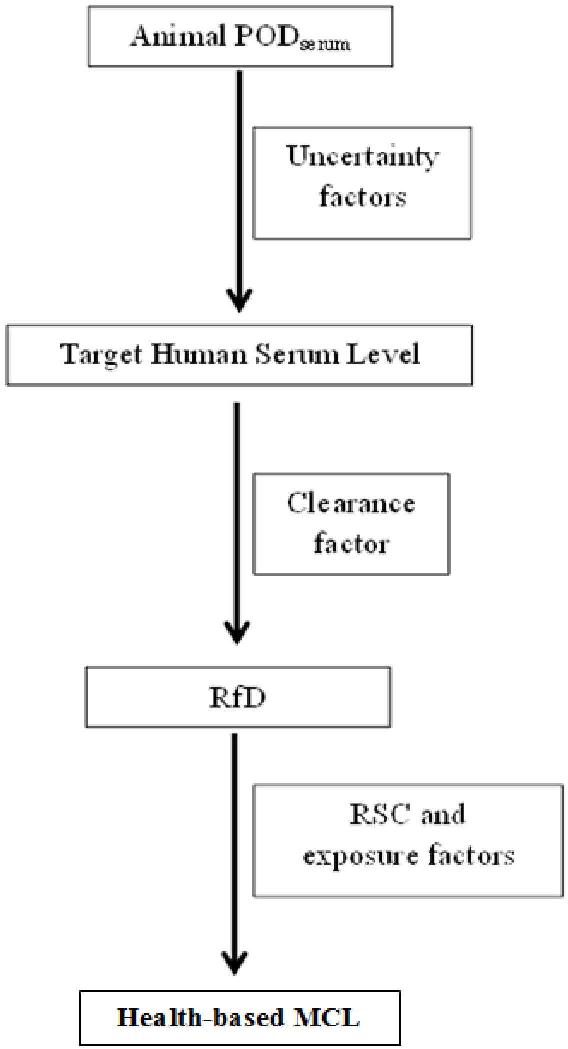
Mode of Action

- Immune effects
  - Possible role for PPARα
    - In contrast to hepatic effects, no data suggesting lack of relevance to humans
  - Other potential modes of action
- Developmental/fetal effects
  - Observed effects do not necessarily share same MOA
  - Developmental effects, including neonatal mortality, following gestational PFOS exposure are PPARα-independent
  - Possibly, PFOS interference with lung surfactant and other proposed MOAs

Mode of Action - Carcinogenicity

- Hepatocellular tumors
  - PFOS does not appear to be genotoxic or mutagenic
  - Evidence indicates minor role, if any, for PPARα dependent MOA
  - No evidence to suggest lack of human relevance
- Thyroid follicular cell tumors
  - No evidence to inform possible MOA
  - Considered relevant to humans in risk assessment

Health-based MCL Derivation



Identification of Most Sensitive Non-cancer Endpoints

- Dose-response analysis focused on health endpoints from subset of animal studies:
  - Exposure durations greater than 30 days
  - Shorter-term reproductive and developmental studies involving exposure during gestation and/or the immediate post-natal period
  - Reporting of serum PFOS concentrations at relevant timepoints
- Considered endpoints with LOAELs in the lower end of the range of serum PFOS concentrations (lowest quartile)

Identification of Most Sensitive Non-cancer Endpoints - continued

- In the lowest quartile, the maximum LOAEL serum PFOS was 24,000 ng/ml
- Clustering of animal endpoints with LOAEL serum PFOS ≤ 10,000 ng/ml
- Endpoints at or below this concentration were considered most sensitive animal endpoints (n=21)
- Further exclusions were made for study-specific concerns and/or lack of biological significance
- Four endpoints were carried forward for non-cancer dose-response analysis:
  - Increased relative liver weight, adult mice (Dong et al., 2009)
  - Increased relative liver weight, adult mice (Dong et al., 2012a)
  - Increased hepatocellular hypertrophy, adult rats (Butenhoff et al., 2012)
  - Decreased plaque forming cell response, adult mice (Dong et al., 2009)

Dose Response Analysis
Non-cancer endpoints

- Based on serum PFOS concentrations (internal dose) rather than administered dose
- Dose-response investigated using USEPA benchmark dose modeling (BMD) software (ver. 2.6.0.1)
- Fitting and assessing benchmark dose model fit follows USEPA guidance
- If data did not support BMDL development, NOAEL or LOAEL used as point of departure (POD)

Points of Departure

- Two of four non-cancer endpoints provided acceptable fits and BMDL derived. Other two endpoints based on NOAEL

Reference	Endpoint	Basis of POD	POD (ng/ml)
Dong et al., 2009*	Increased relative liver weight	BMDL	5,585
Butenhoff et al., 2012	Increased hepatocellular hypertrophy	BMDL	4,560
Dong et al., 2012a	Increased relative liver weight	NOAEL	4,350
Dong et al., 2009	Decreased plaque forming response	NOAEL	674

- Two studies of same endpoint: Dong et al., 2012a is more sensitive than Dong et al., 2009 (dropped from further consideration)

Target Human Serum Levels

- Analogous to Reference Dose (RfD) but in terms of internal dose rather than administered dose.
- $POD_{(PFOS\ serum)}$ / Uncertainty Factors = Target Human Serum Level

Endpoint and Reference	Uncertainty Factors (UF)	UF Total	POD (ng/ml)	Target Human Serum Level (ng/ml)
Heptacellular hypertrophy, 2 years (Butenhoff et al., 2012)	3 – interspecies toxicodynamics 10 – sensitive subpopulations	30	4,560	152
Liver weight, 60 days (Dong et al., 2012a)	3 – interspecies toxicodynamics 10 – sensitive subpopulations 3 – subchronic duration	100	4,350	43.5
Plaque forming response, 60 days (Dong et al., 2009)	3 – interspecies toxicodynamics 10 – sensitive subpopulations	30	674	22.5

Development of RfDs from Target Human Serum Levels

- Clearance factor is a constant which relates human serum levels to administered doses such as RfDs
- Used to develop RfDs from Target Human Serum Levels
- USEPA derived clearance factor for PFOS of 8.1×10^{-5} L/kg

Endpoint and Reference	Target Human Serum (ng/ml)	RfD (ng/kg/day)	RfD (mg/kg/day)
Heptacellular hypertrophy (Butenhoff et al., 2012)	152	12.3	1.23×10^{-5}
Liver weight (Dong et al., 2012a)	43.5	3.5	3.5×10^{-6}
Plaque forming response (Dong et al., 2009)	22.5	1.8	1.8×10^{-6}

Relative Source Contribution Factor (RSC)

- Accounts for non-drinking water sources including food, soil, air, water, and consumer products
- Default value for RSC is **20%**
  - 20% of total exposure is assumed to come from drinking water
  - And 80% from non-drinking water sources
- If supported by available data, a higher chemical-specific value (up to 80%) can be used
  - Insufficient data to develop chemical-specific RSC for PFOS
  - No New Jersey specific biomonitoring data (U.S. - NHANES)
  - PFOS occurs in public water more frequently in NJ than in US overall
  - Communities with contaminated drinking water may also have more exposure from non-drinking water sources such as dust, contaminated soil, or other environmental media
  - Recreationally caught fish from contaminated waters may be important exposure source
- Default of 20% also implicitly accounts for higher exposures in infants than older individuals

Potential Health-based MCL Calculation

- Default exposure assumptions: 2 L/day drinking water consumption, 70 kg adult body weight, and 20% RSC
- Calculation: $$\text{Health-based MCL (ng/L)} = \left(\frac{\text{RfD (ng/kg/day)} \times \text{Body weight (kg)}}{\text{Daily drinking water intake (L/day)}} \text{ x RSC} \right)$$

Endpoint and Reference	Target Human Serum Level (ng/ml)	RfD (ng/kg/day)	Health-based MCL (ng/L = ppt)
Heptacellular hypertrophy (Butenhoff et al., 2012)	152	12.0	84
Liver weight (Dong et al., 2012a)	43.5	3.5	25
Plaque forming response (Dong et al., 2009)	22.5	1.8	13

Health-based MCL Recommendation

- Based on decreased plaque forming cell response in mice (Dong et al., 2009)
  - Well established toxicological effect of PFOS – four positive studies and only one negative study.
    - Identified as sensitive and relevant endpoint in several other scientific evaluations of PFOS
  - Appropriate basis for risk assessment
    - Indicator of decreased immune function and potential disease risk
    - Used as basis for EPA IRIS risk assessments of other chemicals
  - Supported by epidemiological evidence for analogous effect in humans - decreased vaccine response
- Lowest of the potential Health-based MCLs for non-cancer effects
- **Recommended Health-based MCL is 13 ng/L**

Weight of Evidence for Carcinogenicity

- Weight of Evidence Descriptor: *Suggestive Evidence Of Carcinogenic Potential*
- Only one study assessed carcinogenic potential:
  - Chronic (2 year) rat study (Butenhoff et al., 2012)
- Increased incidence of:
  - Hepatocellular tumors in males (high dose only) and females
  - Thyroid tumors in male recovery group only (exposed to high dose for 1st year, not exposed for 2^{nd} year)

Estimation of Cancer Risk

- Concluded that cancer risk estimates are too uncertain for use as basis of Health-based MCL
- Thyroid tumor data not appropriate for dose-response modeling
- Hepatocellular tumor data from females support cancer slope factor development
  - Slope factor from males highly uncertain - tumors only at high dose
  - Slope factor based on female data is 9.0×10^{-6} $(ng/kg/day)^{-1}$
  - Uncertainties include inclusion of recovery group data and dose metric based on area under the curve (AUC) serum levels
- At the recommended Health-based MCL of 13 ng/L, lifetime cancer risk was estimated as 3 in one million
  - Close to cancer risk goal for New Jersey MCLs of one in one million

Uncertainties

- Health effects are associated with general population-level exposures to PFOS, indicating a need for caution about additional exposure from drinking water.
  - Importantly, continued human exposure to even relatively low concentrations of PFOS in drinking water results in elevated serum PFOS concentrations. These elevations are greater in infants, a sensitive subpopulation for PFOS's effects
- Associations of PFOS with health effects in communities with contaminated drinking water have not been studied
- Potential additive toxicity of PFOS and other PFCs that may co-occur in NJ drinking water was not considered.

Recommended Health-based MCL is 13 ng/L (0.013 µg/L).

Comparison to USEPA Health Advisory

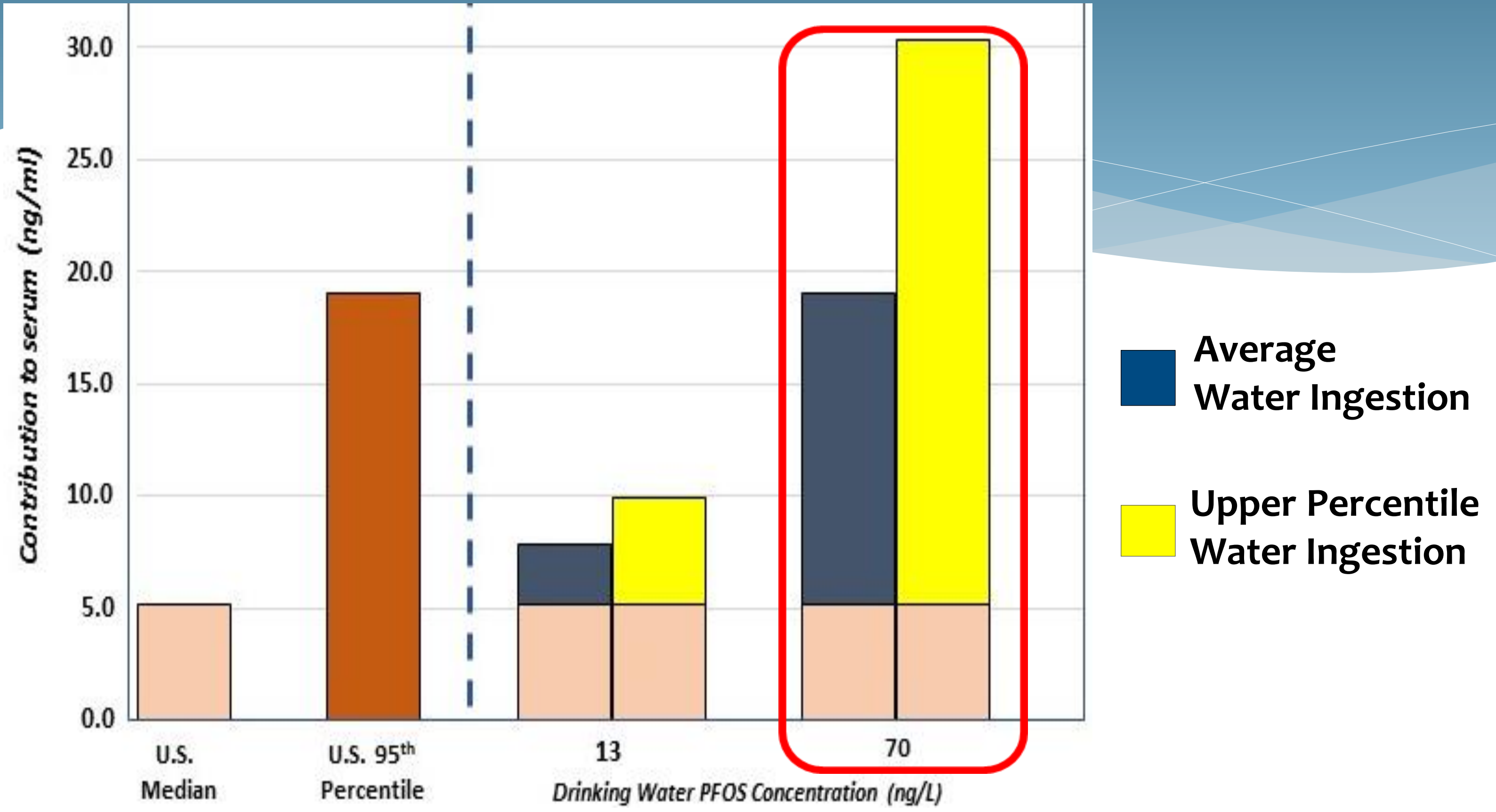
Parameter	USEPA Office of Water (OW) Lifetime Health Advisory	DWQI Draft Health-based MCL Recommendation
Drinking Water Concentration	**70 ng/L** **(applies to total of PFOS & PFOA)**	**13 ng/L**
Reference Dose (RfD)	20 ng/kg/day (2 x 10^{-5} mg/kg/day)	1.8 ng/kg/day (1.8 x 10^{-6} mg/kg/day)
	Based on decreased body weight in neonatal rats (F_2 generation)	Based on decreased plaque forming cell response in adult male mice
Interspecies conversion	Based on pharmacokinetic modeling used to predict average serum PFOS concentrations.	Based on measured serum PFOS concentrations at end of dosing period.
Estimated lifetime cancer risk at Health Advisory /Health-based MCL	Not assessed by EPA. Estimated as 2 x 10-5 based on DWQI cancer slope factor	Estimated as 3 x 10-6 based on DWQI cancer slope factor
	“suggestive evidence of carcinogenic potential”	
Relative Source Contribution Factor	20%. To account for non-drinking water exposures. .	
Assumed Drinking Water Consumption	0.054 L/kg/day; 90th percentile for lactating woman	0.029 L/kg/day; Based on NJDEP default upper percentile adult assumptions: 2 L/day, 70 kg

Comparison to USEPA Health Advisory – Endpoint Selection

Endpoint (study)	Administered dose at LOAEL (mg/kg/day)	Serum PFOS concentration at LOAEL (ng/ml)
USEPA - ↓ neonatal body weight (Luebker et al. 2005)	0.4	25,000 Predicted average over exposure duration
DWQI - ↓ plaque forming cell response (Dong et al., 2009)	0.083	7,132 Measured at terminal sacrifice

- Lower LOAEL for ↓ plaque forming cell response than ↓ neonatal body weight, based on both administered dose and internal dose
- USEPA acknowledges that ↓ plaque forming cell response is consistently found in animals, and that concerns for adverse immune system effects are supported by human data
- Rationale for USEPA precluding ↓ plaque forming cell response for use in risk assessment is unclear to Health Effects Subcommittee

Increase in Serum PFOS Predicted from USEPA Health Advisory (70 ng/L)



- Predicted increases of ~4-fold with average ingestion; ~6-fold with upper percentile (2 L/day)
- Greater increases in infants, a sensitive subpopulation for PFOS effects
- Increases in serum levels not considered by USEPA.