

**U.S. Environmental Protection Agency Response to
New Jersey Drinking Water Quality Institute (DWQI) Health Effects Subcommittee
Draft Health-Based Maximum Contaminant Level Support Document:
Perfluorooctanoic Acid (PFOA) Appendix 2 – Comparison of USEPA Office of Water Health
Advisory and DWQI Recommended Health-Based MCL for PFOA**

November 21, 2016

BACKGROUND

On May 25, 2016 EPA published final lifetime drinking water health advisories (HA) for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). EPA developed the health advisories to assist federal, state, tribal and local officials, and managers of drinking water systems in protecting public health when these chemicals are present in drinking water. The health advisories, which identify the concentration of PFOA and PFOS in drinking water at or below which adverse health effects are not anticipated to occur over a lifetime of exposure, are: 0.07 parts per billion (70 parts per trillion) for PFOA and PFOS. Health advisories are non-regulatory and reflect EPA's assessment of the best available peer-reviewed science. States may choose to develop different HA or guideline values based on their own analyses, including more stringent values.

In 2014, EPA's draft health effects support documents (HESD) for PFOA and PFOS underwent an independent, contractor-led, scientific panel peer review and public comment. The draft documents and charge questions for the expert peer review panel were prepared by EPA to ultimately develop drinking water health advisories for PFOA and PFOS. The goal of the expert peer review was to ensure that EPA's interpretations of toxicological studies and their conclusions were reasonable, sound, and consistent with the underlying science, and that, as a whole, the documents were clear and scientifically credible.

The expert peer review process for EPA's draft HESDs for PFOA and PFOS followed the process recommended in its 2013 guidance, *Conflict of Interest (COI) Review Process for Contractor-Managed Peer Review*. Three Federal Register notices were published: the first notice called for public nominations of experts to serve on the panel peer review and announced the public release of the draft HESDs, the second notice published a preliminary list of peer reviewers and invited the public to comment, and the third notice announced the final peer reviewers and logistics and procedures for participating in the public peer review meeting. Public comments received during the comment period were provided to the peer reviewers for their consideration during their review of the HESDs prior to their panel meeting on August 21-22, 2014.

EPA revised the HESDs based on comments from the expert peer reviewers and the public and used them as the basis to develop the 2016 lifetime health advisories for PFOA and PFOS in drinking water.

To address criticisms of EPA's drinking water HA for PFOA made by the New Jersey Drinking Water Quality Institute (NJ DWQI) Health Effects Subcommittee in their June 27, 2016 public review draft document, *Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)*, specifically *Appendix 2 – Comparison of USEPA Office of Water Health Advisory and DWQI Recommended Health-Based MCL for PFOA*, EPA is providing the responses below. These comments

are being provided to make clear the scientific basis described in the 2016 EPA lifetime HA for PFOA and are not intended to critique the NJ DWQI proposed value.

DERIVATION OF THE REFERENCE DOSE (RfD)

NJ DWQI stated that some toxicological endpoints (e.g. persistent liver toxicity from developmental exposures and delayed mammary gland development) were not considered in EPA's non-cancer risk assessment for PFOA.

NJ DWQI stated that EPA did not consider the hepatic effects from developmental exposure studies in developing the PFOA health advisory. NJ DWQI considered persistent liver toxicity from developmental exposures to very low doses of PFOA (Filgo et al., 2015; Quist et al., 2015) but concluded that these endpoints could not be used as the basis for an RfD because the serum PFOA data needed for dose response modeling were not provided. NJ DWQI stated that these studies give further indication of effects at doses lower than those that lead to increased liver weight, the primary basis for their recommended RfD.

NJ DWQI stated that EPA's reasons for not considering the mammary gland endpoint (mode of action not known, effects occurred only at higher doses in a second strain of mice, functional significance is unclear) are not scientifically valid and/or are also equally or more applicable to the endpoints selected as the basis for the HA (see comments on critical study below).

EPA developed two supporting documents that describe the science supporting the 2016 HAs for PFOA and PFOS. These documents can be found at <https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos>. Studies focused on liver effects by both Filgo et al. (2015) and Quist et al. (2015) are discussed extensively in EPA's HESD for PFOA. One of the major recommendations made by the expert external peer review panel that reviewed EPA's draft HESDs was that EPA follow the criteria established by Hall et al. (2012) in the evaluation of the adversity of liver endpoints. In the case of PFOA, EPA's assessment shows that liver weight and hypertrophy endpoints do not meet the criteria for adversity (see HESD section 4.1.1). Increased liver weight is acknowledged as a common finding, but not considered adverse in the absence of other effects as defined by Hall et al. (2012). Thus, EPA selected the critical endpoint that reflects adverse effects in the developing fetus and newborn as the most sensitive effect to serve as the basis for the derivation of the RfD.

Studies focused on mammary gland development in animals following exposure to PFOA are described in EPA's HESD for PFOA (see Sections 3.2.7 and 3.3.3). Researchers focused on effects resulting from indirect exposure of offspring via treatment of pregnant animals and/or direct exposure of peripubertal animals starting about the time of weaning. These studies show effects on mammary gland morphology (branching and bud growth) in pups at low doses. However, EPA did not select delayed mammary gland development as the critical effect for PFOA for several reasons, including ambiguity regarding the qualitative component of the scores and lack of observed effects on body weight of pups nursing from affected dams (White et al., 2011), and no differences in response to lactational challenge (White et al., 2011).

EPA examined a multitude of effects observed in the available animal studies. EPA modeled data from multiple studies of various durations which observed adverse effects including development (delayed ossification, accelerated puberty, pup body weight), body and kidney

weight, liver, and immune endpoints. Section 4 of EPA's HESD for PFOA (USEPA 2016) describes consideration of these studies and endpoints and selection of the critical study and effect that serves as the basis of the RfD for PFOA.

EPA's candidate RfDs for PFOA are based on multiple adverse effects resulting from short-term and longer-term exposures, and fall within a narrow dose range. Based on the consistency of the responses across the chronic studies and those for reproductive and developmental endpoints, and with recognition of the use of developmental toxicity as the most sensitive critical endpoint, EPA selected 0.00002 mg/kg/day as the RfD for PFOA. This value is based on the human equivalent dose (HED) for developmental effects (reduced ossification in male and female pups and accelerated puberty in male pups) from the Lau et al. (2006) study.

The RfD that serves as the point of departure (POD) for EPA's lifetime HA is also applicable for effects other than those occurring during development. The candidate RfDs derived from the two-generation study by Butenhoff et al. (2004) for effects on adult body weight and kidney weights in F0 and F1 male rats is the same as the value based on the developmental effects observed by Lau et al (2006). The candidate RfD from the DeWitt et al. (2008) study for suppression of the immunological response to a challenge is the same as that from Lau et al. (2006).

Additionally, candidate RfDs (see Table 4-9 in the HESD for PFOA) derived from other studies (Wolf et al., 2007 and Perkins et al., 2004) identifying developmental body weight effects and liver necrosis also support the selection of the RfD derived from Lau et al. (2006) as these derived candidate RfDs are greater than 0.00002 mg/kg/day.

Therefore, EPA selected the RfD based on Lau et al. (2006) as protective for adverse developmental, immunological, renal effects, as well as liver effects categorized as adverse by Hall et al. (2012).

Additionally, Lau et al. (2006) observed effects following in utero and lactational exposures to PFOA, identifying the pregnant and lactating women as the populations of greatest concern for adverse effects following exposure to PFOA. Thus, due to the potential increased fetal and neonate susceptibility during the time period of pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime health advisory for this target population during this potential critical time period.

CRITICAL STUDY EVALUATION

NJ DWQI stated that the long term consequences and functional significance of the effect on ossification in the Lau et al. (2006) study are unclear and thus question the use of this endpoint as the basis for the RfD for PFOA. NJ DWQI stated that the delayed ossification and puberty delay in Lau et al. (2006) are developmental delays and not adverse effects.

The Lau et al. (2006) study provides the results from two separate groups of dams and neonates. The first group is the source of the data for reproductive outcomes and fetal teratology. For this group, the pups were sacrificed at birth. The doses of 5, 10, 20 and 40 mg/kg/day resulted in statistically significant incidence of full litter resorptions (26 to 100 percent). Thus, these results limit the evaluation of the pups to the lowest doses tested, 1 and 3 mg/kg/day. Both of those dose

groups had significantly reduced ossification of the proximal forelimb phalanges. Ossification sites were reduced compared to controls for the hindlimb phalanges as well, with the difference significant for the 1 mg/kg/day dose. The confidence bounds on the ossification sites depicted in Lau et al. (2006) are wide, demonstrating considerable variability among test organisms. Significantly increased limb deformations at birth for doses ≥ 5 mg/kg/day suggest that the effects at the lower doses are more than simple developmental delays. Lau et al. (2006) indicated that the delay in ossification was not a simple developmental delay because it was present at birth and in the absence of a body weight effect.

NJ DWQI indicates that there is another study in a different strain of rat that shows there are strain differences in sensitivity for the ossification effect. The fact that the Yahia et al. (2010) study reported delayed ossification in a different strain of rat on PND 4 supports EPA's selection of the Lau et al. (2006) study and ossification delay as the critical effect rather than simply a manifestation of strain differences. There was no significant effect at a dose of 1 mg/kg/day in that study ($1.1 \pm 1.1\%$ of the pups) compared to controls ($2.5 \pm 2.5\%$), but there was a pronounced ossification delay for doses of 5 mg/kg/day ($15.9 \pm 12.4\%$) and 10 mg/kg/day ($47.7 \pm 17.2\%$) with wide confidence bounds similar to those reported by Lau et al. These effects were accompanied by other adverse effects, including reduced body weight and mortality during the 4-day observation period.

Although NJ DWQI concluded this result did not support the delayed ossification effects at 1 mg/kg/day, EPA notes differences in reporting of the endpoint between Lau et al. (2006) and Yahia et al. (2010). Lau et al. (2006) reports the mean number ossification sites per pup while Yahia et al. (2010) reports the percent of pups identified as exhibiting a delay but does not describe the basis for that determination. The fact that the identified LOAEL from Lau et al. (2006) represents an effect that was not accompanied by decreases in pup weight or mortality supports EPA's identification of 1 mg/kg/day as a preferred POD for analysis.

The observation of delayed puberty came from the second group of pups evaluated by Lau et al. (2006) where a different group of dams were exposed during gestation and lactation. At doses ≥ 5 mg/kg/day pup mortality was also observed ($\geq 30\%$ at day 3). For both the 1 and 3 mg/kg/day doses, the mean preputial separation day was significantly lower than that for the controls. Lau et al. (2006) stated that delayed puberty occurred in the absence of effects on body weight and was indicative of an effect on development. Although the mean days for preputial separation begin to increase for the 5 and 10 mg/kg/day dose groups they remained statistically different from controls. About 70% of the pups died before the time of preputial separation days for the 10 mg/kg/day dose group and 90% died from the 20 mg/kg/day dose group.

INTERSPECIES CONVERSION IN RfD DEVELOPMENT

NJ DWQI states that the effects that EPA chose from the Lau et al. (2006) study do not follow a typical monotonic dose response curve in which greater effects occur with increasing external dose and are not appropriate for dose-response analysis based simply on a NOAEL or LOAEL.

EPA employed a peer-reviewed pharmacokinetic model (Wambaugh et al., 2013) that utilized the serum measurements from animal studies in mice, monkeys and rats to determine average serum values (a hybrid of the animal area under the curve [AUC] and modeled serum) to be used

as points of departure for calculating HEDs. This model utilized species specific physiological features to normalize the impact of pharmacokinetic differences that underlie the species difference in half-lives. The modeled human average serum was converted to a HED by taking into account the human half-life and volume of distribution and applying the standard equation for a first order reaction to solve for clearance at the point where there is a balance between human intake and excretion (steady state). The fundamental principle supporting this approach is the steady state concept that there is a point where all species achieve a balance between intake and elimination described as steady state. This approach was supported by the expert peer review panel that reviewed EPA's draft HESD in 2014.

Estimates of the percent of steady state achieved at the exposure duration when the animals were sacrificed and the serum NOAEL and/or LOAEL (mg/L) for the critical effects were projected using standard pharmacokinetic principles (pages 4-11 and 4-13 of the HESD). The duration associated with the effect and its accompanying percent of steady state were considered when selecting the uncertainty factor (UF) for exposure duration.

The human clearance in terms of L/kg_{bw}/day was calculated from the human volume of distribution and half-life. The average serum estimate was then multiplied by the human clearance value to calculate the HED in units of mg/kg/day. This calculation gave a single value that represented all humans. A ten-fold UF for intrahuman variability was applied to adjust for pharmacokinetic and pharmacodynamic differences among humans. Support for this UF comes from Bartell et al. (2010), where the highest serum value for a population that had been highly exposed did not exceed the mean value by more than a factor of 10.

The strength of the EPA approach is its ability to harmonize the pharmacokinetic variables across the three animal species and predict average serum values applicable to humans at the serum levels where effects (or no effects) were observed and is superior to benchmark dose modeling of dose response for a chemical with nonlinear pharmacokinetics. The concordance across the potential RfDs derived from the modeled studies after adjusting for uncertainties provides strong support for EPA's RfD and the assessment of critical effects.

CONSIDERATION OF EPIDEMIOLOGICAL DATA

NJ DWQI rejects some of the reasons that EPA used to support not using the epidemiology data in a quantitative manner (i.e. to derive the RfD).

EPA's HESDs and health advisories include presentation of the epidemiological data and a discussion of limitations in its use quantitatively at this time (Section 8.2 of the HA and Sections 3.1.1.12, 3.1.2.1 and 4.1.1 of the HESD). These reasons are summarized below:

- The epidemiology data are of greatest value in identifying the effects of concern. In the case of PFOA there is good correlation between some of the human and animal data for a number of the effects (serum lipids, immunological responses, neonatal growth, testicular and kidney tumors). In other cases, the data are more consistent with conditions that decrease excretion or increase retention of PFOA, thereby elevating serum values, or potentially leading to reverse causation (e.g. low glomerular filtration rates, age at menarche and menopause).

- An inability to determine dose or exposure duration for the serum measurement as it relates to appearance of the effect observed, thus minimizing the suitability of using the one-time serum value for its role in causing a measured chronic effect. One example is the case of an increase in total cholesterol, a condition widely distributed among humans and with strong associations with diet, body weight, genetics and many life-style features that are difficult to control in an analysis.
- The impact of other PFAS compounds on the observed effects is a factor that must be considered given the number of epidemiology studies that reported statistical associations with the serum measurement for more than one of the detected PFAS.

CONSIDERATION OF INCREASES IN SERUM PFOA LEVELS FROM EXPOSURE TO DRINKING WATER

NJ DWQI stated EPA does not acknowledge that increases in serum PFOA levels expected from exposure to 70 ng/L can easily be predicted. NJ DWQI concludes that prediction of human serum levels from drinking water concentrations is technically sound and not subject to debate. NJ DWQI also stated that EPA does not acknowledge that multiple human health effects are consistently associated with serum levels below those expected from exposure to 70 ng/L in drinking water.

The EPA pharmacokinetic model (described in Section 4.1.1.1 in the HESD) and the equation applied to obtain the HED from the modeled average serum are based on the current scientific understanding of the mathematical relationship between dose, distribution, metabolism and excretion (e.g. pharmacokinetics) as it applies to steady state conditions. EPA believes that use of the guideline value (70 ppt or 14 ppt) in the equation for human clearance to determine its impact on human serum levels is inappropriate. The guideline values are based on toxicity values where a point of departure (a HED in the case of EPA's PFOA assessment) and uncertainty factors are taken into account. Accordingly, use of this value decreases the model average serum estimate by a factor of 100 (total uncertainty factor, $UF_H^{0.5} + UF_A^{0.5} + UF_L^{10}$). The uncertainty factors are unrelated to the pharmacokinetic parameters utilized in model development. The WHO/IPCS (2010) guidelines on the application of physiologically-based pharmacokinetic models in risk assessment state that the models are logically constrained to the range of doses for which the model was evaluated (e.g. tested/validated). Therefore, the clearance equation cannot justifiably be utilized to predict serum values for humans using a guideline value (70 ppt or 14 ppt) that is well below the range of doses and serum values utilized in the derivation of the model.

The EPA Health Advisory applies to potable drinking water systems with current drinking water concentrations that exceed 70 ppt. Any treatment or remediation measures taken to reduce exposures will lead to decreasing exposures from the water source and result in a decline in serum levels for all individuals currently at steady state, unless exposures from other media replace what has been removed by treatment of the public water supply. EPA stands by the analysis that exposure to drinking water at the lifetime HA value of 70 ppt is predicted to maintain a steady state level of PFOA/PFOS in serum that will not result in adverse effects in the general population.

SENSITIVE SUBPOPULATIONS

NJ DWQI states that EPA developed a lifetime HA for the general population (adults ages 21 and older) of 100 ng/L or 100 ppt and that EPA indicated that this value is protective for effects other than developmental toxicity. NJ DWQI also commented that EPA states that sensitive subpopulations are pregnant and lactating women, and bottle-fed infants, but does not include women who plan to become pregnant.

EPA's HA for PFOA is 70 ppt and this is the only recommendation provided. Due to the potential increased susceptibility during the time period of pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime HA for this target population during this potential critical time period. EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90th percentile for lactating women (see Table 3-81 in USEPA 2011). Comparing the pregnant woman and adults in the general population including women who may become pregnant and those who are pregnant, the lactating woman is the more protective scenario given her increased water intake rate for her body weight needed to support milk production. As a comparative analysis, EPA calculated a lifetime HA value for alternative exposure scenarios for the general population (see Section 8.5 of the HA). Calculation of a lifetime HA value for the general population (adults ages 21 and older) is 0.1 µg/L, assuming a drinking water rate of 2.5 L/day and a mean body weight of 80 kg.

CANCER RISK

NJ DWQI stated that EPA's calculation of the cancer risk assessment did not consider the longer half-life in humans than rats.

EPA used the linear multistage model and a body weight adjustment to account for conversion between animals and humans to determine HED for derivation of the cancer slope factor. Following EPA guidance (cite), the body weight to the $3/4$ adjustment is made on the basis of the fact that body weight to the $3/4$ is a surrogate for body surface area differences and body surface area is a general predictor for basal metabolic rate (BMR). BMR plays a substantial role in inter-individual pharmacokinetics. The HED adjusted for body weight was used along with the response rate (a 4% increase in the cancer risk, a value that falls in the range of observation) to develop the cancer slope factor. The derivation of the cancer slope factor for PFOA is presented in Section 4.2 of the HESD for PFOA (USEPA 2016).

EPA's approach differs from the approach presented by NJ DWQI where no correction based on the body weight ratio was applied. In its place, NJ DWQI applied a 120-fold uncertainty factor accounting for the difference between a half-life in humans and rats.

There is an acknowledged difference in the half-life for animals and humans (7 days for rats and 2.3 years for humans). However, half-life should only be considered as a tool to adjust for species differences as it relates to the lifespan. Rats live an average of about 2 years (the time at which the animals were sacrificed in the Butenhoff et al. 2012 study). By policy, the EPA considers the human lifespan to be 70 years. When one uses the half-life to lifespan ratio for an interspecies adjustment, for the rats the ratio of half-life to life span is 0.01 (7 days ÷ 730 days = 0.01). For a human the ratio is (2.3 years ÷ 70 years) = 0.03. The human ratio is 3 times greater

than the animal ratio ($0.03 \div 0.01 = 3$). The body weight adjustment made by EPA has the same impact on the concentration associated with a E-6 risk for cancer as would an adjustment based on the human versus rat half-life to lifespan ratio of 3. Both would lead to an approximately 3-fold reduction in risk. Thus, the EPA adjustment adequately reflects an adjustment for the rat to human differences.

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