Agency for Toxic Substances and Disease Registry (ATSDR)
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Perfluorohexanesulfonic Acid (PFHxS)
January 2023
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ATSDR would like to thank EPA for the opportunity to review their draft PFHxS review documents. ATSDR finds the text well-written throughout most of the review and the charge questions appropriate for peer review; however, ATSDR has also identified some important concerns that need to be addressed in the assessment in relation to the approach taken for RfD derivation. Overall, ATSDR agrees with an approach to consider epidemiological studies in the derivation of health effect values and agrees with the consideration of the thyroid endpoints for the derivation of health effect values; however, ATSDR has some concerns that the chosen minimal critical effect (1/2 standard deviation or 5% decrease in antibody response to the tetanus vaccine from the Grandjean et al. studies) and methods used to derive EPA's PFHxS subchronic and lifetime exposure RfDs may result in health effect values that are artificially low.

ATSDR recognizes that the EPA OW and EPA IRIS operate independently on their PFAS assessments; however, inconsistencies with the approach taken to derive reference doses in the PFAS assessments between IRIS and the updated OW assessments (for PFOS and PFOA) send mixed signals and highlight the uncertainty which plagues PFAS risk assessments. Additionally, ATSDR would like to point out that the approach taken to derive subchronic and chronic RfDs for PFHxS by IRIS has remained almost identical to the approach taken to derive subchronic and chronic RfDs for PFDA. ATSDR has not received a full technical response to the interagency comments submitted for the PFDA toxicity assessment in March 2022, and ATSDR shares many of the same comments and concerns on this PFHxS assessment.

1. The clinical relevance of a 5% decrease (1/2 standard deviation) in an antibody response to the tetanus vaccine needs to be clarified, and this effect seems minimal. We recognize that EPA defaults to a BMR of ½ SD for developmental or 1 SD for all other effects in the absence of information regarding the level of change that is considered biologically significant; however, it is well known that, in a normal vaccine response, there is already a wide distribution in the levels of titers considered normal. Changes of 30% or more in antibody titers can be within normal variations of IgG for the general population. We suggest that EPA strengthen its rationale behind choosing this value/effect.
    a. ATSDR suggests that changes in IgG may only be clinically relevant if the magnitude of change is 2 standard deviations and changes are noted in more than one antibody (Agarwal and Cunningham-Rundles. 2007. Assessment and Clinical Interpretation of Reduced IgG Values). CDC notes that the clinical efficacy for tetanus toxoid and diphtheria is virtually 100%.
        i. In the Budtz-Jørgensen and Grandjean (2018) study, all children had clinically protective antibody titers regardless of PFAS exposure (defined by WHO as higher than 0.1 IU, whereas basic immune protection is

defined by the range >0.01-0.09 IU). The study did not report an increase in the rate of tetanus infections.

b. The lack of sufficient evidence for an increase in infections associated with PFHxS exposure supports the uncertainty regarding the use of decreased antibody responses for the derivation of health guidance values. Although EPA emphasizes the small number of studies that found higher odds of infectious disease with PFHxS exposure, it is important to note that the evidence is mixed and unclear. Recent PFAS evaluations/reports from ATSDR (2021), NASEM (2022), and WHO (draft, 2022) have not suggested an association between PFHxS and/or PFAS exposure and risk of infection.
    i. ATSDR 2021 (Toxicological Profile for Perfluoroalkyls): "In general, the available studies do not suggest an association between serum PFHxS and decreased infectious disease resistance."
    ii. The recent NASEM report (National Academies of Sciences, Engineering, and Medicine. 2022. Guidance on PFAS Exposure, Testing, and Clinical Follow-Up) concluded "there is inadequate or insufficient evidence of an association between PFAS exposure and risk of infection." No clinical recommendations were made regarding alterations in antibody titers.
    iii. WHO 2022 (PFOS and PFOA in Drinking-water): "In summary, it is suggested that decreased antibody response to vaccination may lead to reduced immune system functionality. However, studies report inconsistencies in the relationship between PFAS exposure and infection propensity in early life (Antoniou et al., 39 2022; ATSDR, 2021; EFSA, 2020; Steenland et al., 2020; US EPA, 2021a; 2021b) and therefore, the clinical relevance of these findings is unclear. More studies, particularly with more objective measures of infections, are needed (EFSA, 2020)."

c. Upon consultation with a vaccine subject matter expert in CDC, ATSDR adds the following questions:
    i. It needs to be clarified what 5% (1/2 SD) means in the context of log-transformed units. A change in the population titers (such as 1.0 IU/mL to 0.95 IU/mL) does not consider that these correspond to log-transformed serum dilutions. We recommend EPA explain how to interpret a "5% change in titers" given this distribution.
    ii. It is unclear if the benchmark calculations are appropriate for target values with wide and non-gaussian distributions. Anti-tetanus titers as shown in several studies follow a bimodal distribution in most age groups, with a significant minority having very high titers (probably due to receipt of booster vaccination at an emergency room visit; Grandjean et al., 2017) and the remainder contained within an apparently log-normal distribution with wide confidence intervals (e.g. Schauer et al, 2003; Grandjean et al., 2017); e.g., 4-8 year-olds had a geometric mean titer of 0.8 IU/ml with 3rd/97th percentiles ranging from 0.09-12.87 (Schauer et al., 2003). The calculations in Budtz-Jørgensen and Grandjean (2018) assume a point value for the geometric mean titer of the population. EPA should address

if these calculations are appropriate if they don't consider confidence intervals. Due to the wide confidence intervals associated with log-normal distribution, even studies investigating titers in immunocompromised patients will report a 50% reduction in titers that does not reach statistical significance.

d. ATSDR has some concerns regarding the experimental design of Budtz-Jørgensen and Grandjean (2018) and EPA's choice to use this study.
    i. Was the life-span of specific IgG considered in the model?
    ii. Can you explain the discrepancy regarding why the decreased antibody response was only associated with PFAS (age 5) after the tetanus booster (antibodies measured at age 7) and not during the initial series of vaccines? The association between decreased antibody response and PFHxS was only noted between child PFHxS exposure at 5 years of age and antibody titers at 7 years of age (booster was given at age 5). There was no effect of PFHxS exposure during the first 3 doses of the Tetanus vaccine (most crucial doses). The maternal PFHxS exposure would have been higher than the child PFHxS exposure at 5 years of age.
        1. The concept of the Developmental Origins of Health and Disease (DOHaD) states that perinatal exposure may affect the normal development that will later result in a health effect. Immune system development in a human starts during the first months of gestation and continues to mature after birth. Intrauterine exposure may disturb crucial functions of the immune system during critical fetal development, leading to immune dysfunction in offspring.
        2. Grandjean et al. 2012 and Budtz-Jørgensen and Grandjean 2018 report that PFAS, such as PFHxS, will affect the antibody response to the tetanus vaccine booster given at age 5, resulting in decreased serum antibodies 2 years later.
        3. Based on all the above premise, one would expect that maternal exposure would negatively hamper the immune response to vaccine immunization with the first dose (priming) given at 3 months of age and repeated inoculation given at ages 5 and 12 months (Grandjean et al. 2012). However, this is not the case, based on the results from tables 3 and 4 of Grandjean et al. 2012 (original data used by Budtz-Jørgensen and Grandjean 2018).
        4. ATSDR also has some concerns the effect may be transient at 5 years of age and thus nonsignificant.
    iii. The study is missing crucial information such as the vaccine status of the mother and data on the maternal-specific anti-tetanus IgG levels.
        1. Newborns have transplacental IgG from the mother which protects the infant during the first three months of life. Tetanus is rare, and placental anti-toxin IgG transfer is the protective factor in neonatal tetanus prevention. In fact, maternal vaccination with tetanus is recommended as public health effort to decrease neonatal tetanus

in the US and worldwide (Murphy et al. 2008, WHO 2019). These antibodies may interfere negatively with early vaccination.
2. Unscheduled or undisclosed boosters (such as during emergency visits) may influence anti-tetanus and anti-diphtheria titers.

2. EPA indicates Budtz-Jørgensen and Grandjean (2018) accounts for exposure to multiple PFAS; however, the analysis performed in the study only addresses co-exposure to PFOA and PFOS. Outside of PFAS, the study only addresses two additional contaminants (PCBs and mercury). Confounders from other PFAS and other chemicals are a major concern for the use of any epidemiological study for PFAS health effect values. Additionally, some PFAS have a very short half-life and clear more quickly, and as a result, evaluated health effects may be partially attributed to PFAS with longer half-lives. How is EPA determining that the effects observed are due to the PFAS in question (e.g., PFHxS) and not a different, correlated PFAS (or another chemical)? EPA only minimally addresses this issue in the assessment. ATSDR recommends that EPA strengthen this rationale.
    a. For example, Timmerman et al., (2022) acknowledges that environmental chemicals, specifically other PFAS, were strongly correlated and could not be easily separated. Therefore, the authors suggested that the "focus should be on general trends in the results rather than a single significant finding." Although this study found an association between diphtheria/tetanus antibodies and some contaminants, "the association vanished or was reversed after adjustment for potential confounders, especially area of residence." Philippe Grandjean was also an author of this study. In Budtz-Jørgensen and Grandjean (2018), the authors note that the measurement of exposure to specific PFAS remains imprecise.
    b. This same issue is relevant to non-PFAS chemicals as well.
        i. The same population from Budtz-Jørgensen and Grandjean (2018) has been studied extensively for immunotoxicity stemming from exposures to other PFAS, PCBs, DDT, mercury, etc.
        ii. A recently published study ongroundwater of the Eastern United States (McMahon et al. 2022) found that "Concentrations of tritium, chloride, sulfate, DOC, and manganese + iron… were significantly higher in samples containing PFAS detections than in samples with no detections.".
3. Associations between PFAS and decreased antibody titers in medium or high confidence studies are mainly from limited authors and limited children/adolescent cohorts. As noted in the PFHxS assessment, additional studies evaluating this association are of low confidence.
    a. ATSDR recommends EPA comment on the appropriateness and practicality of applying Budtz-Jørgensen and Grandjean (2018) for current environmental PFAS exposure. Please address the criteria used to determine if these studies will fit the general population and comment on the practicality of using mother/infant pairings (pregnancy to 5 or 7 years of age) to develop lifetime exposure values.
    b. The cohort from Budtz-Jørgensen and Grandjean (2018) eat a diet containing a large quantity of seafood. It is unclear how nutrition and other social

determinants, which are important for health and can affect immune homeostasis, were accounted for in these studies.

4. ATSDR would like EPA to comment if the modeling from Budtz-Jørgensen and Grandjean 2018 was independently validated. ATSDR is under the impression that the authors could not provide the data from these studies.
5. Considering the endpoint (decreased anti-tetanus antibodies) is the most sensitive endpoint, the study population reflects developmental vulnerability, the 5% antibody decrease (1/2 SD) is minimal and has unknown clinical implications, an uncertainty factor of 3 for database limitations was used, and an uncertainty factor of 10 for human variability was utilized, ATSDR is concerned a combination of factors have collectively led to a subchronic and lifetime RfD for PFHxS that is artificially low.
    a. It needs to be clarified why EPA chose to use a chronic study to derive a subchronic RfD when high-confidence subchronic studies were available and considered candidates.
    b. The immune effects from Budtz-Jørgensen and Grandjean 2018 result in an RfD that is significantly lower than the other candidate for RfD derivation. ATSDR has concerns that guidance values from this group of studies using the same study population may be an outlier.
    c. Given the combined availability of candidate animal and epidemiological studies from PFHxS and read-across data from other PFAS, ATSDR disagrees with EPA's use of an uncertainty factor of 3 for database limitations.
6. The list of authors and contributors to the PFHxS assessment appeared to represent a range of expertise, but individuals with a medical degree were missing from the list. Were any medical professionals consulted in the development of this assessment and associated RfDs, particularly in relation to the clinical relevance of the identified sensitive endpoints? ATSDR recommends consulting medical professionals with clinical experience, particularly vaccine immunologists and endocrinologists, to strengthen the discussion over the use of these critical effects.
7. As stated earlier, ATSDR recognizes that the EPA OW and EPA IRIS conduct their PFAS assessments separately; however, ATSDR believes it is important to evaluate individual PFAS in a consistent manner.
    a. In the November 2021 *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA/PFOS,* the EPA OW utilized the same critical effects and study (Budtz-Jørgensen and Grandjean 2018) for the derivation of PFOA and PFOS RfDs. Only a lifetime RfD was derived for each. Following the SAB panel review and public comment period, the critical effect was changed from the decreased antibody response to a combination of 4 different critical effects, and the value of the RfDs increased. Budtz-Jørgensen and Grandjean 2018 is no longer the sole study utilized for those RfDs, and ATSDR recommends that EPA IRIS also reconsider the approach taken to derive the PFHxS RfDs.
        i. It is unclear how the updated RfDs (PFOA/PFOS from OW and PFDA from IRIS) based on Budtz-Jørgensen and Grandjean 2018 were derived and if the use of this study for the derivation of the PFHxS RfDs was

consistent with the updated approach used for the other RfDs (PFOA, PFOS, and PFDA).

ii. Although not relevant to the current PFHxS assessment by IRIS, if IRIS should decide to reconsider and alter the approach for the derivation of PFHxS RfDs to follow an approach similar to the EPA OW for PFOS/PFOA, ATSDR recommends EPA thoroughly address the clinical relevance of each critical effect.

1. As mentioned above, ATSDR recommends EPA provide a more detailed discussion on the clinical relevance of the decreased antibody response. In addition, decreased birth weight, changes in liver enzymes and changes in cholesterol levels associated with PFAS exposure all have uncertainties regarding clinical relevance. These health effects have not been associated with clinical disease following PFAS exposure.

b. The evaluation of health effects has been inconsistent between reviews of different PFAS species. For instance, the PFDA assessment from EPA IRIS reviewed by ATSDR in early 2022 did not consider the thyroid effects relevant to human health, but both the PFBA and this PFHxS review consider the effects relevant. ATSDR recommends that EPA remain consistent across health effects and PFAS species or provide additional discussion to justify the inconsistency between assessments.

8. ATSDR agrees there are not enough data to evaluate the carcinogenicity of PFHxS nor are there enough data to derive RfC values.
9. ATSDR recommends EPA comment on the ability of current analytical methods to detect PFHxS at the level of the draft RfDs.

Sources

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