3568 Systemic and immunotoxicity induced by topical application of perfluorohexane sulfonic acid (PFHxS) in a murine model

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Background and Purpose: Per- and polyfluoroalkyl substances (PFAS) are a large group (over 12,000) of synthetic surfactants with unique chemical and physical properties including water and oil resistance and heat and corrosion stability. Due to these properties, PFAS are incorporated into the manufacturing of both consumer and industrial products including food packaging, textile coatings, fire-retardant foams, firefighter personal protective equipment, cleaners, wood glue, ski wax, leather, nonstick cookware, carpets, and construction material and more recent studies have found applications of PFAS to include cosmetics, personal care products, hand sanitizers, and makeup removers. However, these properties due to their strong carbon-fluorine bond, make these chemicals resistant to degradation and allow them to accumulate in the environment and in humans, leading to environmental and human health concerns. Perfluorohexane sulfonic acid (PFHxS) is a 6-carbon chain PFAS with a long half-life (4.7-35 years in humans) that has been detected in human samples. Despite the high potential for occupational and environmental dermal exposure, dermal exposure studies are lacking. To help fill in this knowledge gap, the present study aims to investigate systemic effects of dermal exposure of PFHxS in a murine model. **Methods:** The present study analyzed organ weight, serum chemistries, histology, immune phenotyping, gene expression, and spleen and serum IgM response to sheep red blood cells (SRBC) to evaluate the systemic and immunotoxicity of sub-chronic 28- or 10-day dermal exposure of PFHxS (0.625-5% or 15.63-125 mg/kg/dose). **Results:** Elevated levels of PFHxS were detected in the serum and urine, suggesting that absorption is occurring through the dermal route. Liver weight (% body) significantly increased and spleen weight (% body) significantly decreased with PFHxS exposure, which was supported by histopathological changes. Additionally, PFHxS significantly reduced the humoral immune response and altered immune subsets in the spleen, suggesting immunosuppression. Gene expression changes were observed in the liver, skin, and spleen with genes involved in fatty acid metabolism, necrosis, and inflammation. Immune-cell phenotyping identified significant decreases in B-cells, NK cells, and CD11b+ cells in the spleen along with increases in CD4+ and CD8+ T-cells, NK cells, and neutrophils in the skin. **Conclusions:** These findings support dermal PFHxS-induced liver damage and immune suppression similar to those reported for oral PFAS exposure. Unique mechanisms of toxicity are suggested between PFHxS and other PFAS previously studied. Further investigation into PFAS dermal exposure is needed to understand the hazards of skin exposure on systemic toxicity and immune function. Overall, this data raises concern about PFAS dermal exposure and suggest the need for further examination.

3569 A Comparison of *In Vitro* and *In Vivo* Points of Departure with Human Biomonitoring Levels for Per- and Polyfluoroalkyl Substances (PFAS)

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Background and Purpose: Per- and polyfluoroalkyl substances (PFAS) are widely used in non-stick coatings, firefighting foams and other products. Their fluorinated state contributes to their unique uses and stability, but also may result in long half-lives in the environment and humans. There is increasing evidence that some of these compounds can be toxic, leading to immunosuppression, cancer, and other unwanted outcomes. Hundreds to thousands of PFAS are in commerce and the environment, but only a small fraction of these have been evaluated for toxicity using standard *in vivo* tests. This leads to a need to prioritize which of these compounds should be examined further. Here we demonstrate an approach to prioritizing PFAS by combining human biomonitoring data (blood concentrations) with bioactivity data (concentrations at which bioactivity is observed) from a battery of *in vitro* assays. The result is a risk metric, the margin of exposure (MoE) which is the bioactivity concentration divided by the blood concentration. Chemicals with low MoE values could then be prioritized for further risk assessment or risk management. **Methods:** We have combined *in vitro* points of departure from a separate study on ~150 PFAS with blood levels taken from a comprehensive literature survey and calculate MoE values. A total of 31 PFAS had all required data. **Results:** Two of these (PFOA and PFOS) have MoE values <1 for some populations. An additional 9 PFAS have MoE values <100 for some populations. **Conclusions:** We provide a discussion of multiple sources of uncertainty in the MoE calculation and conclude that this complete set of 11 PFAS with MoE<100 should be examined further. This study shows a promising approach to screening level risk assessments of compounds such as PFAS that are long-lived in human and other species and provides an approach for further studies being carried out at the US EPA. *Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the US EPA.*

3570 Children's Health Data Gaps Identified by EPA's PFAS Toxicity Assessments: A Case for Future Research Needs

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Background and Purpose: Per- and polyfluoroalkyl substances (PFAS) are a class of chemicals known for their ubiquitousness in the environment, persistence in the body, and associations with negative health effects. The U.S. Environmental Protection Agency (EPA) has conducted human health toxicity assessments and derived toxicity values (i.e., reference doses, or RfDs) for several PFAS. Building upon the research agenda for PFAS, this effort seeks to refine the understanding of data needs for children's health endpoints. **Methods:** EPA human health toxicity assessments for several PFAS (e.g., PFHxA, PFBA, PFBS, HFPO-DA (GenX), and PFPrA) were reviewed and available data and studies were compiled to highlight areas with research needs specific to children's health. **Results:** The published assessments have considered all available epidemiologic, toxicological, and carcinogenicity studies available and generated RfDs for non-cancer health effects when the available database is robust and adverse endpoints can be identified for dose-response analysis. However, lack of data often prevents derivation of RfDs for a variety of health effects. For example, most of the assessed PFAS had few or no available epidemiologic or toxicological studies for nervous system effects. Further, only a portion of the available data reviewed in these documents are derived from studies that investigated the consequences of developmental exposure to PFAS, resulting in uncertainties regarding children's health. For instance, few or no developmental and early life exposure studies of PFAS exposure have investigated domains such as endocrine and thyroid effects. **Conclusions:** Several organ systems across multiple PFAS lack epidemiological and toxicological studies that focus on developmental exposure windows. Future research can aid in addressing the identified children's health gaps to facilitate risk assessment efforts by the U.S. EPA.*The views and opinions expressed here do not reflect official US Environmental Protection Agency Policy.*

3571 New Approach Methodology (NAMs) Based Approach For Relative Toxicity Factors of PFAS in Risk Assessment

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Background and Purpose: Several per- and polyfluoroalkyl substances (PFAS) have been detected in environmental media at hazardous waste sites. There is limited PFAS toxicity information and regulatory thresholds available for use during hazard identification, human health risk assessments, and when characterizing a site and making risk-management decisions. EPA's traditional approach is to derive toxicity values using results from *in vivo* studies. There is significant uncertainty with the results of a risk assessment when several of the detected PFAS lack toxicity values. EPA's 2021 *National PFAS Testing Strategy* and *Framework for PFAS Mixtures* documents highlight the need to evaluate the growing list of PFAS and recommend incorporating the recent advancements in new approach methodologies (NAMs) for assessing toxicity. The generalized read-across (GenRA) NAM tool available on EPA's CompTox dashboard and the U.S. Department of Health and Human Services National Toxicology Program (NTP) Integrated Chemical Environment (ICE) tool for toxicokinetic adjustments can be used to estimate the relative toxicity of PFAS without regulatory toxicity values. **Methods:** A NAMs-based approach was used to estimate relative toxicity factors (RTFs) (i.e., toxicity relative to PFOA or PFOS for selected endpoints) for six PFAS without regulatory toxicity values (PFHpA, PFPeA, PFDoA, PFPeS, PFHpS, PFDoS). Relative toxicity factors using this NAMs-based approach were also calculated for four PFAS (PFHxA, PFBA, PFDA, PFBS) with available EPA toxicity values and compared with relative toxicity values derived from EPA toxicity documents. The following approach was used: • Step 1—Surrogate chemicals for target PFAS (i.e., PFAS without toxicity values) were identified using structural categories consistent with those used in EPA's 2021 Testing Strategy and structural similarity indices (SIs) based on biologically relevant structural features in the GenRA tool (https://comptox.epa.gov/dashboard/). • Step 2—The SIs were used in combination with *in vivo* toxicity data for the surrogates from EPA toxicity documents, and a toxicokinetic adjustment across surrogates and targets using steady-state serum concentration predicted by the NTP ICE tool to estimate the potential toxicity of target PFAS. The toxicity estimates were based on one of two selected endpoints in this step: hepatic or developmental. The potential toxicity estimates for the target PFAS were compared with EPA toxicity estimates for PFOA or PFOS to estimate RTFs for target PFAS (relative to PFOA or PFOS). • Step 3—The NAM-based RTFs for PFAS with available EPA toxicity values were compared with relative toxicity values derived from EPA toxicity documents. **Results:** For three target PFAS (PFPeA, PFHpA, and PFDoA), the RTFs (relative to PFOA) for the hepatic endpoint were 0.01, 0.08, and 47, respectively. For the remaining three target PFAS (PFPeS, PFHpS, and PFDoS), the RTFs (relative to PFOS) for the developmental endpoint were 0.01, 1.2, and 27, respectively. The predicted RTFs for the three PFAS with EPA toxicity values and in the perfluorocarboxylic acid category (PFHxA, PFBA, and PFDA) were within an order of magnitude (0.2- to 6-fold) of the relative toxicity derived from EPA's toxicity documents. For the one PFAS in the perfluorosulfonic acid category (PFBS), the predicted RTF was within two orders of magnitude (75-fold) of the relative toxicity derived from the

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