UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: 30 December 2020

SUBJECT: OCSPP senior toxicologist review of the draft document titled "Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)

TO: David Fischer, M.P.H., J.D.
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention

Purpose

Senior Toxicologists in the Office of Chemical Safety and Pollution Prevention (OCSPP) were asked by the OCSPP Deputy Assistant Administrator to review the Office of Research and Development's (ORD) draft document titled "Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)" (hereinafter the "PFBS document").

OCSPP's current review focused on the animal to human dosimetry, the benchmark response level, and the application of uncertainty factors used for calculating the oral reference doses in the PFBS document and provided perspectives on whether OCSPP would apply such uncertainty factors under the Toxic Substances Control Act (TSCA). Specifically, OCSPP commented on the interspecies (UF_A), LOAEL-to-NOAEL (UF_L), subchronic-to-chronic (UF_S), and database deficiency (UF_D) uncertainty factors. In each instance, with the exception of the UF_D, OCSPP there was agreement with the ORD applied UF values. The rationale for OCSPP's conclusions is provided below.

Animal to Human Dosimetry

A dosimetry adjustment used on p. 69 of the PFBS document, which is based on the ratio of the elimination half-life of PFBS in animals to humans. This adjustment was performed this using the following equation and values:

HED = point of departure (POD) × $t_{1/2}$ mouse (4.5 hrs) ÷ $t_{1/2}$ human (1,050 hrs)

This approach is consistent with how the Office of Pollution Prevention and Toxics (OPPT) evaluates perfluorinated chemicals under TSCA with the exception of methodological differences (*i.e.*, benchmark margin of exposure [MOE] approach versus reference dose derivation).[1] For example, OPPT replaces the default value of 3.16 for the toxicokinetic (TK) component of the interspecies uncertainty factor with the estimated blood half-life of the perfluorinated chemical in humans by the half-life in animals (*i.e.*, TK = 1,050 hrs ÷ 4.5 hrs = 233) when deriving the benchmark MOE. In comparison, ORD applied the dosimetric adjustment to the applied dose levels, prior to performing benchmark dose modeling, and then applied uncertainty factors to the BMDL. The interspecies TK component was reduced to 1 in the PFBS calculations, since the dose levels were dosimetrically adjusted.

Benchmark Response (BMR)

ORD derived reference doses based on the results of Feng *et al*. (2017), which showed decreased serum total T4 in mouse dams dosed with PFBS on gestational days 1 through 20 and their offspring on postnatal days 1, 30, and 60. On p. 68 of the PFBS document, it states "as there is no clear or consistent biological threshold for T4 changes specifically associated with untoward developmental health outcomes, a BMR of 0.5 SD was identified as a default when performing BMD modeling on thyroid hormone alternations in offspring, consistent with EPA *BMD Technical Guidance* [reference omitted]."

OCSPP notes that the Office of Pesticide Programs (OPP) stated the following under its considerations for evaluating Endocrine Disruptor Screening Program Tier 1 Assays: "the developing nervous system is dependent on adequate amounts of thyroid hormones, and neurological impairments can potential occur when the deficiency is present during brain development. Thus, an approximate 20% increase in TSH or decrease in thyroxine (T4) is generally considered to be toxicologically relevant. As with all other endpoints, changes in thyroid hormones (manifested as changes in TSH and/or T4) as well as histopathology and organ weight changes should be considered in context with the totality of the data in determining whether an effect is adverse."[2]

Since the Agency established a toxicologically relevant benchmark for the endpoint used by ORD for deriving its reference doses, OCSPP recommends that ORD either provide a justification for not using this benchmark, consider using this benchmark in lieu of the applied default, or at a minimum include BMD modeling with a BMR of 20% for comparative purposes.

[1] EPA (2015) Subject: RAD Standard Operating Procedure: Data-Derived Extrapolation Factor for Interspecies Extrapolation of Toxicity Data for Perfluorohexanoic acid (PFHxA); From: Director, Risk Assessment Division (RAD); To: HazRATT; Through: Management Liaison, HazRATT; Date: December 22, 2015; 11 pp., at p. 2.

[2] EPA (2013) Endocrine Disruptor Screening Program Tier 1 Assays: Considerations for Use in Human Health and Ecological Risk Assessments, Office of Pesticides Program, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), 16 pp., at p. 6.

Interspecies (UF_A)

OCSPP concurs with the value of 3 and rationale for applying this value when deriving the reference doses, as discussed on pp. 29 and 77 of the PFBS document.

LOAEL-to-NOAEL (UF_L)

OCSPP concurs with applying a value of 1, since benchmark dose modeling was used for deriving the points of departure.

Subchronic-to-Chronic (UF_S)

OCSPP concurs with applying a value of 1, given that the principal study evaluated the developmental period, which is recognized as a susceptible life stage.

Database Deficiency (UF_D)

Application of the default 10-fold factor for UF_D for the subchronic and chronic reference doses, respectively, may not be warranted based on the rationale provided below.

For the subchronic reference dose, on p. 77 of the PFBS document the justification for applying a 3-fold factor for UF_D is provided: "the observation of decreased thyroid hormone is known to be a crucial element during developmental life stages, particularly for neurodevelopment, and the database is limited by the lack of developmental neurotoxicity studies. In addition, as other health effect domains such as immunotoxicity and mammary gland development are effects of increasing concern across several members of the larger PFAS family [references omitted] the lack of studies evaluating these outcomes following PFBS exposure is a limitation in the database."

OCSPP notes that deficits in thyroid hormone are a precursor event to the potential for adverse effects on the developing brain. Therefore, protecting against the thyroid effects, as done in the PFBS document, would protect against potential adverse effects on the developing brain, thereby obviating the need for developmental neurotoxicity studies. This approach is consistent with EPA's shift with its testing focus from the developmental neurotoxicity test guidelines "to more targeted testing based on commonly accepted modes of action".[3]

OCSPP performed a search on the Health Assessment Workspace Collaborative (HAWC) database for primary (*e.g.*, bone marrow and thymus) lymphoid organs and for mammary gland under the open field for "Organ".

[3] EPA (2020) The Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment, FIFRA Scientific Advisory Panel, Virtual Preparatory Meeting, August 25, 2020, 20 slides, at slide 4, available at: https://downloads.regulations.gov/EPA-HQ-OPP-2020-0263-0033/content.pdf

For bone marrow, six assessment endpoints were retrieved on HAWC from a 28-day oral toxicity study performed by NTP (2018); however, no points of departure were listed.[4] Therefore, OCSPP reviewed the NTP (2018) study, which reported hypocellularity of the bone marrow in male (10/10) and female (9/10) rats in the 1,000 mg/kg-day groups.[5] This effect was not observed in any of the rats in the lower dose groups (*i.e.*, 62.6, 125, 250, or 500 mg/kg-day).

For thymus, 44 assessment endpoints were retrieved on HAWC from a 10-day oral toxicity study performed by 3M (2000), a 28-day oral toxicity study performed by 3M (2001), a 28-day oral toxicity study performed by NTP (2018), a 90-day oral toxicity study performed by Lieder *et al*. (2009), and a two-generation oral toxicity study performed by Lieder *et al*. (2009).[6] The lowest point of departure for absolute and relative thymus weight was a NOAEL of 250 mg/kg-day for male/female rats in the 28-day oral toxicity study performed by NTP (2018). All other points of departure exceeded this value.

For mammary gland, four assessment endpoints were retrieved on HAWC from a 28-day oral toxicity study performed by NTP (2018).[7] The NOAEL for male and female rats for non-neoplastic lesions in the mammary gland was 1,000 mg/kg-day.

The above findings suggest that primary lymphoid organs and mammary glands are not target organs following subacute exposures in the rat. Though the reported measures may not be comprehensive evaluations for the spectrum of effects that may occur on the immune system or mammary glands, the absence of adverse effects on these organs would explain why more definitive studies were not performed. Further, a LOAEL from the 28-day oral toxicity performed by NTP (2018) was identified on p. 48 of the PFBS document as 62.6 mg/kg-day, based on "Decreased T3, free T4, total T4 in males and females. Increased relative liver weight in females, and increased relative right kidney weight in males."

For the chronic reference dose, on p. 79 of the PFBS document the justification for applying a 10-fold factor for UF_D is provided: "However, as thyroid hormone is known to be critical during developmental life stages, particularly for neurodevelopment, the database is limited by the lack of developmental neurotoxicity studies. Further, due to the lack of chronic duration studies, there is additional uncertainty

[4] HAWC (2018) Filtered endpoint search for "bone marrow" under the open field for "Organ", available at: https://hawcprd.epa.gov/ani/assessment/100000037/endpoints/?studies_0=&chemical=&cas=&lifestage_exposed=&lifestage_assessed=&species_0=&species_1=&strain_0=&strain_1=&data_extracted=&name=&system=&organ=Bone+Marrow&effect=&effect_subtype=&tags=&dose_units=&order_by=animal_group__experiment__study__short_citation&paginate_by=

[5] NTP (2018) NTP Technical Report on the Toxicity of Perfluoroalkyl Sulfonates (Perfluorobutane Sulfonic Acid, Perfluorohexane Sulfonate Potassium Salt, and Perfluorooctane Sulfonic Acid) Administered by Gavage to Sprague Dawley (HSD:Sprague Dawley SD) Rats, NTP TOX 96, U.S. Department of Health and Human Services, National Toxicology Program (NTP), 165 pp., at pp. 32-33.

[6] HAWC (2018) Filtered endpoint search for "thymus" under the open field for "Organ", available at: https://hawcprd.epa.gov/ani/assessment/100000037/endpoints/?studies_0=&chemical=&cas=&lifestage_exposed=&lifestage_assessed=&species_0=&species_1=&strain_0=&strain_1=&data_extracted=&name=&system=&organ=thymus&effect=&effect_subtype=&tags=&dose_units=&order_by=animal_group__experiment__study__short_citation&paginate_by=&page=2

[7] HAWC (2018) Filtered endpoint search for "mammary gland" under the open field for "Organ", available at: https://hawcprd.epa.gov/ani/assessment/100000037/endpoints/?studies_0=&chemical=&cas=&lifestage_exposed=&lifestage_assessed=&species_0=&species_1=&strain_0=&strain_1=&data_extracted=&name=&system=&organ=Mammary+Gland&effect=&effect_subtype=&tags=&dose_units=&order_by=animal_group__experiment__study__short_citation&paginate_by=

regarding how longer-term exposures might impact hazard identification and dose response assessment for PFBS via the oral route (e.g., potentially more sensitive effects). Lastly, as immunotoxicity and mammary gland development are effects of increasing concern across several members of the larger PFAS family [references omitted], the lack of studies evaluating these outcomes following PFBS exposure is a limitation in the database."

As noted above, OCSPP does not view the lack of developmental neurotoxicity studies as a limitation to the database that warrants application of a value greater than 1 for the UF_D, given that the reference doses in the PFBS document were derived on precursor effects (*i.e.*, decreased thyroid hormone) to potential adverse effects on the developing brain.

OCSPP agrees that the absence of chronic duration studies represents a data gap and would recommend a value of 3 to account for this.

OCSPP does not concur with the statements that immunotoxicity and mammary gland development are additional data gaps that warrant application of a 10-fold factor, based on the previously stated rationale.