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November 8, 2021

U.S. Environmental Protection
EPA Docket Center (ORD Docket)
Mail Code: 28221T
1200 Pennsylvania Ave NW
Washington, DC 20460

RE: IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid
EPA Docket: EPA-HQ-ORD-2020-0675
FRL-8870-01-ORD

The National Tribal Toxics Council (NTTC) appreciates the opportunity to provide comments on the IRIS toxicological review of Perfluorobutanoic Acid (PFBA). NTTC is an EPA Tribal Partnership Group (TPG), supported by the Office of Pollution Prevention and Toxics (OPPT), that works to provide Tribes with information on issues and rulemakings related to toxic chemicals and pollution prevention. On behalf of Tribes, the NTTC works to ensure that tribal risks are accurately characterized and evaluated in EPA's risk assessment process by informing and educating the EPA on tribal lifeways, exposures, and risks.

The NTTC is particularly interested in how sensitive subpopulations are considered in toxicological assessments, especially populations with systematic health disparities that influence chemical dose-response relationships. Thus, we focused on how the IRIS Toxicological Review of PFBA and Related Salts (Review) evaluated toxicity for sensitive groups.

Overall, we have two lines of concern—1) Insufficient consideration is given to the inhalation exposure route and an outstanding need exists to derive inhalation parameters or otherwise compensate for data gaps, and 2) Derived reference doses are not adequately protective of tribal people as a susceptible subpopulation.

PFBA Inhalation Related Concerns

The NTTC is concerned that the PFBA Review of inhalation exposures is incomplete and was given little consideration. Perez et al. (2013) found that lung samples of human cadavers had higher PFBA concentrations than liver samples and suggested that, because PFBA

is a short chain compound, its predominance in lung tissue of human adults could reflect the inhalation of contaminated dust. Tribal populations are at greater risk of exposure to contaminated indoor dust due to older and disrepaired housing, including ventilation systems, older durable and non-durable products with greater wear and tear, and occupational settings with less or no OSHA oversight due to size of business and remoteness, and self-employment and working from home (Pindus et al. 2017, US Census 2019). Further, tribal populations are disproportionately exposed to untreated emissions from open burning of municipal waste, including multiple products containing PFBA. Over 40 percent of tribes reside in Alaska, where contained open burning of the waste stream is the primary authorized waste management method (ADEC 2021). The large majority of tribal homes are well within one mile of these facilities, a distance where adverse associated health outcomes have been documented (Gilbreath 2006, Gilbreath & Kass 2006). Further, while not authorized under state regulations as in Alaska, open burning of trash is a common practice for households throughout Indian Country and rural America. PFBA is found in fly and bottom ash of standard high temperature waste incinerators, although it tends to release more in leachate (Liu 2021). However, Solo-Gabriele et al (2020) found that PFBA, as well as total PFAS, decreased in waste ash leachate samples with decreasing incinerator operation temperatures, meaning that PFBA emissions with open burning, which is carried out at temperatures that are less than those considered to be effective at destroying PFAS, may be of significantly greater magnitude.

Of great concern and a topical point is that Danish researchers (Grandjean et al 2021) recently demonstrated a link between patients who experience more severe cases of COVID-19 and exposure to PFBA, possibly due to immunotoxicity effects. Tribal populations have been severely impacted by COVID-19. For example, according to new source-based data, American Indian or Alaska Native individuals were 3.5 times more likely to be hospitalized with the virus (NCHS 2021). The incidence, prevalence, morbidity, and mortality of COVID-19 in tribal communities are considered to have "amplified health inequities in American Indian communities because of underfunded and under-resourced health systems, limited access to health services, poor infrastructure, and underlying health disparities" (JHU 2021). The burden to allostatic load and immunosuppression, which may further add to health disparities, is discussed later in these comments.

NTTC in interested in the evaluation of an inhalation reference concentration protective of susceptible subpopulations with underlying disease because lung cancers and COPD have been found to be 9% and 70% higher respectively in tribal populations than the nation as a whole (Laffey et al 2021). COPD prevalence among American Indians and Alaska Natives was 11% in 2011 (Ford et al 2013). With over 1 in 10 tribal people living with COPD, the NTTC is concerned that the incidence of COPD is not explained by ethnicity, but by systemic socioeconomic disparities such as the 81% greater incidence of poverty faced by Native Americans, according to the most recent American Community Survey (Laffey et al 2021). Smoking is a primary contributor and initiating and continuing smoking is also linked to socioeconomic disparities. Education and income level are the primary determinants of smoking (Wang et al 2020) and, at 20%, tribal peoples are nearly twice as likely to not attain a high school education and they have a household income level that is just 70% of white non-Hispanics (Farrigan et al 2020).

The NTTC is concerned that the Review's conclusions about sensitive subpopulations are incomplete. The Grandjean et 2021 study that suggests a possible association of lung related disease and PFBA was not captured by the PFBA Review. No human studies were available to inform the potential for PFBA exposure to affect sensitive subpopulations or lifestages (page 4-4). The Review considers just two sensitivities. A male gender was weighed, but rejected, as a susceptibility despite a sex dependence in some PFBA induced health effects. And due to effects observed in pregnant mice, pregnancy and early life were found to represent two possible sensitive lifestages for

PFBA exposure (page 4-4). This sensitivity was found to be consistent with information across related PFAS compounds (page 3-45).

IRIS assessments need to do a better job in the face of incomplete laboratory data and expand their investigation about the impacts of toxic chemicals to subpopulations beyond life stage, including the health impaired with multiple co-morbidities that may also be at a susceptible life stage. The discussion of potential toxicity in Section 5.2.3 is extremely limited and concludes without any derivation of an Inhalation Reference Concentration, let alone one that considers an inhalation dose response to PFBA for sensitive subpopulations with lung-related health disparities. While physiologically based pharmacokinetic (PBPK) models don't exist, it is NTTC's position that route to route extrapolation should be conducted, using an available model for similar PFAS structures.

An extrapolation also makes sense from an agency efficiency and public protection viewpoint. As the Tribal Partnership Group for OPPT, we naturally look to the near future for a TSCA assessment covering or targeted to PFBA. Clearly, under TSCA, EPA cannot 'kick the can down the road' and again ignore inhalation exposures. Such risk assessments are under a strict timeline and NTTC is concerned that failure to derive an inhalation RfC now will delay the PFBA assessment, which is critical to arrive at risk management decisions protecting tribes and the general population.

Toxicity values from IRIS reviews guide risk assessors here and worldwide. To better avoid inhalation exposures being ignored, as a susceptible subpopulation with potentially higher inhalation exposures, NTTC prefers RfC values with appropriate derivation uncertainty factors versus no reference concentration at all. It is our observation that when chemical behavior is important to general population risk and data are limited or missing, chemical modeling is carried out. All too often, this is not the case for susceptible subpopulation risk, which is left uncharacterized. Adding to the issue, inadequate acknowledgement of this decision and its consequences accompanies such studies, paving the way for risks assessors to leave out not only tribal lifeways, but lifeways of other subpopulations. While there is an appropriate model in the case of PFBA, if the derivation of a parameter of importance to a subpopulation exposure is left out due to lack of data or appropriate models, this advent should be treated as a main headline of the study in order to warn readers that results do not represent subpopulations.

We discuss aspects of equity and toxicity characterization more generally in the next section.

Derivation of Oral Reference Doses

We mention first inregards to Section 1.1.4. The Potential for Human Exposure that, as with inhalation exposures, the tribal population has a potentially higher exposure via release from substandard, unlined and uncovered, product disposal facilities (i.e. landfills) to drinking water. For example, in Alaska about one-third of rural landfills in the State Surface Water Database are within 100 feet of a primary water body used for the community drinking water supply (ADEC 2021).

As the ultimate risk cannot be separated from exposure, and tribal lifeways are woefully underrepresented in risk assessment, it is of particular importance that the reference dose is clearly protective. And particularly because PFBA persists in the environment essentially "forever" and tribes will also persist living in the environment forever, NTTC recommends increasing the uncertainty factors (UF) used in the derivation of the PFBA oral reference doses to those contained in the table below to better compensate for the lack of data on PFBA effects on susceptible

subpopulations. For simplification, NTTC will focus on the overall chronic reference dose in the discussion below, but the concepts apply to the UFs used for the overall, subchronic, acute, and system specific RfDs as well.

Table 1 NTTC Recommended Uncertainty Factors

UF	Current Value	NTTC Recommended value
UFA	3	10
UFH	10	100
UFS	10	10
UFL	1	3
UFD	3	10

We justify our recommendations by referring to the EPA's Review of the Reference Dose and Reference Concentration Processes, authored by the Risk Assessment Forum (RAF) in 2002. It states (emphases added):

> A dose-response analysis for potentially susceptible subpopulations should be done as part of the overall dose-response analysis for health effects in general. "Susceptible" in this context means a differential (greater) response at the same internal dose in a particular segment of the population *due to intrinsic (possibly unknown) factors*. "Susceptible subpopulations" is used here to refer both to life stages *and to other factors that may predispose individuals to greater response to an exposure*. Life stages may include the developing individual before and after birth up to maturity (e.g., embryo, fetus, young child, adolescent), adults, or aging individuals. Other susceptible subpopulations may include people with specific genetic polymorphisms that render them more vulnerable to a specific *agent or people with specific diseases or pre-existing conditions (e.g., asthmatics).* The term may also refer to gender differences, *lifestyle choices*, or nutritional state.
>
> It is important to recognize that little basis currently exists for a priori identification of susceptible subpopulations for many chemicals.

Clearly, the PFBA Review does not evaluate effects for tribal populations. While we cannot supply specific data on PFBA effects on tribes, we provide considerations to support a higher interspecies uncertainty factor (UF_A), higher database UF_D, UF_L, and intraspecies uncertainty factor (UF_H).

UF_A: First, the interspecies or "animal" factor for the chronic oral reference dose should be increased to 10x on the basis of the uncertainty in extrapolating data from healthy and homogeneous rat and mice populations to the human population for susceptible subpopulations. The Review does not discuss this issue, so NTTC assumes it was

not accounted for in assigning a 3X for the UF_A. While it can be argued this aspect can be accommodated in the intraspecies UF_H, NTTC believes it rightfully resides here, to better incentivize research or consideration in extrapolation of healthy animal population effects to health-impaired human effects. As the Risk Assessment Forum states:

> ... healthy animals that are more genetically homogeneous than humans are used in standard toxicity testing protocols, and information on *pre-existing conditions* or genetic polymorphisms *is largely unavailable from animal studies*.

NTTCs questions the use of a 3X factor to derive an RfD that would be fully protective of susceptible populations given the large reliance on mouse and rat studies, in the face of findings from a quantitative and qualitative review of the adequacy of default uncertainty factors carried out by Martin et al (2013). After a review and discussion of multiple comparative multi-species toxicity studies, they conclude:

> In summary, the level of conservatism afforded by the default factor of 10 for interspecies differences depends on the animal species that is considered for analysis. The allometric scaling factor agrees reasonably well with the median of all chemical-specific interspecies factors. Thus, the allometric scaling factor will overestimate interspecies differences for half of the chemicals and underestimate it for the other half. *For rodent species routinely used in chemical hazard assessment, the allometric scaling factors (Table 2) are relatively close to 10, and this value may be exceeded for a sizeable proportion of chemicals.*

UF_D: Additionally, as a subpopulation with disproportionately high consequence of adverse developmental effects (see ACEs discussion below in regards to the seriousness of the effect), the NTTC recommends that the UF_D be increased to 10X. As the review notes in Table 5-5, there is "lack of information on developmental neurotoxicity and other endpoints".

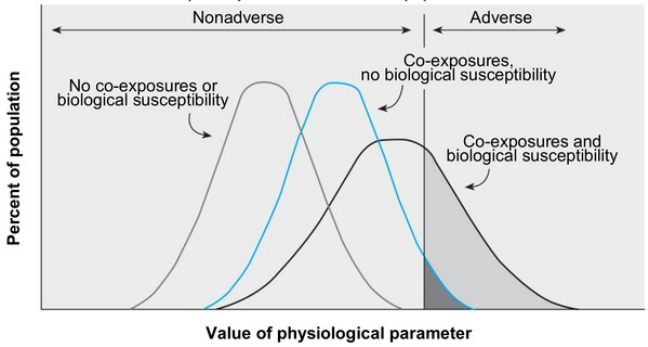
UF_L: NTTC has some concern that NOAELs were considered as endpoints when substantive studies and key European Scientific committees suggest, along with common sense, NOAELs cannot be equated as zero effect levels. Martin et al (2013) discuss this issue at length, arguing that NOAELs can only be used in place of LOAELs if diversity of chemicals which make up human exposures act in strictly independent ways, and at least at that point in time, no mammalian studies demonstrating independent action have been carried out. If combination effects in mammals can be adequately explained by dose addition, combination effects may still occur below dose thresholds associated with zero effects. As a population with a substantial health burden, as well as some differences in gene expression, we are concerned about below dose threshold effects, and therefore recommend a more cautious UF_L of 3X.

UF_H: NTTC strongly calls for an increase in the UF_H used by a *minimum of* 10x to 100x. With sparse data, it is not at all clear that a 10x factor will be protective even of populations unburdened with disease. In evaluating the protection that an uncertainty factor of 10x affords a standard general population of healthy adults of mixed ages and genders, Martin et al (2013) looked at available studies on interindividual toxicokinetic and toxicodynamic variations. They found that for half the chemicals, nearly 8 people in 100,000 would respond to chronic oral exposure -- nearly an order of magnitude over the 1 in 100,000 incidence with 95% confidence level of a minimally adverse response. Martin et al and others, such as Koman et al (2019) state that to consider susceptible subpopulations properly, a multimodal distribution should be employed. However, because toxicity value derivation

primarily assumes a unimodal distribution, the median for the general population should be extended so that a reasonable percentile of the sensitive subgroup is clearly protected. The below excerpted graphic from Koman et al illustrates this point for groups with biological susceptibility.

Tribal health disparities can mean greater population susceptibility.

Fig 1. How coexposures to other chemical stressors and variability in biological susceptibility combine to influence population risk.



Excerpted from Koman PD, Singla V, Lam J, Woodruff TJ (2019) Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. PLOS Biology 17(8): e3000372. https://doi.org/10.1371/journal.pbio.3000372 https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000372

Figure 1.

NTTC agrees with this conclusion as a minimum and as a start in estimating such a median recommends the 100x versus 10x for the UF_H. We should note for future IRIS reviews, that because we believe a 100X factor to be a bare minimum to ensure a 1 in 100,000 protection factor for tribal people, and our peoples are as diverse as the lands on which they derive their lifeways and diets, NTTC prefers a bimodal distribution model to best capture the tribal population.

A 100x UF recommendation is far from spurious and has multiple justifications. The RAF includes several considerations for susceptible subpopulations in assigning a UF_H, including dose-response, seriousness and sub-chronic to chronic and duration /timing effects. For convenience, it is reproduced here:

Table 4-2. Factors for evaluating evidence regarding identification and characterization of susceptible subpopulations[a]

Factor	Increased weight	Decreased weight
Timing (life stage) - response relationship	Effects occur at greater magnitude at one or more life stage(s)	No difference in effects at different life stage(s)
Type of effect	Different types of effects in specific subpopulations	Same effect(s) across all potential subpopulations
Dose-response relationship	Effect occurs at lower exposures in one or more subpopulation(s)	No evidence for differential dose-response across different subpopulations
Latency of effect	Latency to observed effect different in specific subpopulations	No difference between subpopulations in latency to effect
Seriousness/ reversibility of effects	Effects different in seriousness or degree of reversibility in specific subpopulations and/or differences in later consequence of an initially reversible effect	No differences between subpopulations in seriousness and/or reversibility of effects, or in later consequences of an initially reversible effect

[a] Subpopulations may be defined by gender, individuals at different life stages (fetus, child, adult, elderly), differences in genetic polymorphisms, and/or pre-existing diseases or conditions that may result in differential sensitivity to adverse effects from exposure to a specific toxic agent.

Figure 2

NTTC considers the last three of these factors to be paramount in affixing an appropriate RfD protective of tribes.

Dose-Response Relationship

As mentioned above, the Review considers male sex and lifestage as potential sensitive groups. NTTC is concerned that additional consideration was not given to health-impaired subpopulations with health disparities that may result in greater biological response, including liver disease. Partly due to studies focused on aging populations, it is well established that health impairment can impact the outcome of disease and that health impaired individuals may have greater biological response to exposures.

One reason poor health can affect the disposition of the chemical is when organs that are central to elimination of the chemical, like heart, kidney, and liver, are themselves diseased. COPD, which we mentioned above, is at epidemic levels within tribal populations, is associated with alternations of cardiac output, obesity, and Type II Diabetes, which tribal peoples are 50% and 200% more likely to experience (CDC Healthy Tribes Data 2021), are associated with reduced glomerular filtration rates.

Of high concern here is that sensitivity to chemicals can be exacerbated when the target organ of the toxic effect is not only central in its elimination, but is also affected by disease -- here including the liver. In 2018, American Indians/Alaska Natives were **1.6 times more likely to be diagnosed with chronic liver disease** as compared to non-Hispanic whites. The overall death rate for American Indians/Alaska Natives is almost **four times higher** than the non-Hispanic white population. In 2019, chronic liver disease was the fourth leading cause of death for all American Indians/Alaska Natives, and the second leading cause of death for American Indian/Alaska Native men, ages 35-44 (HHS OMH 2021).

An uncertainty factor for the variation of biological response must protect our mothers. American Indian/Alaska Native women are **2.2 times as likely to be diagnosed** with chronic liver disease and **4.8 times more likely to die** from chronic liver disease as compared to non-Hispanic white women. While we are unaware at this time of readily accessible data on pregnancies for those afflicted with liver disease, we are concerned about exposure to PFBA for these women and their developing pre- and postnatal babies, with essentially both facing lifestage and health impairments as susceptibilities.

But tribal population experience multiple susceptibilities beyond liver disease that must also be considered. Tribes experience major health disparities nearly across the board, as the below graphics illustrate. Figure 4 was excerpted from Families USA using CDC data, and Figure 3 is from the Cancer Statistics Working Group and CDC.

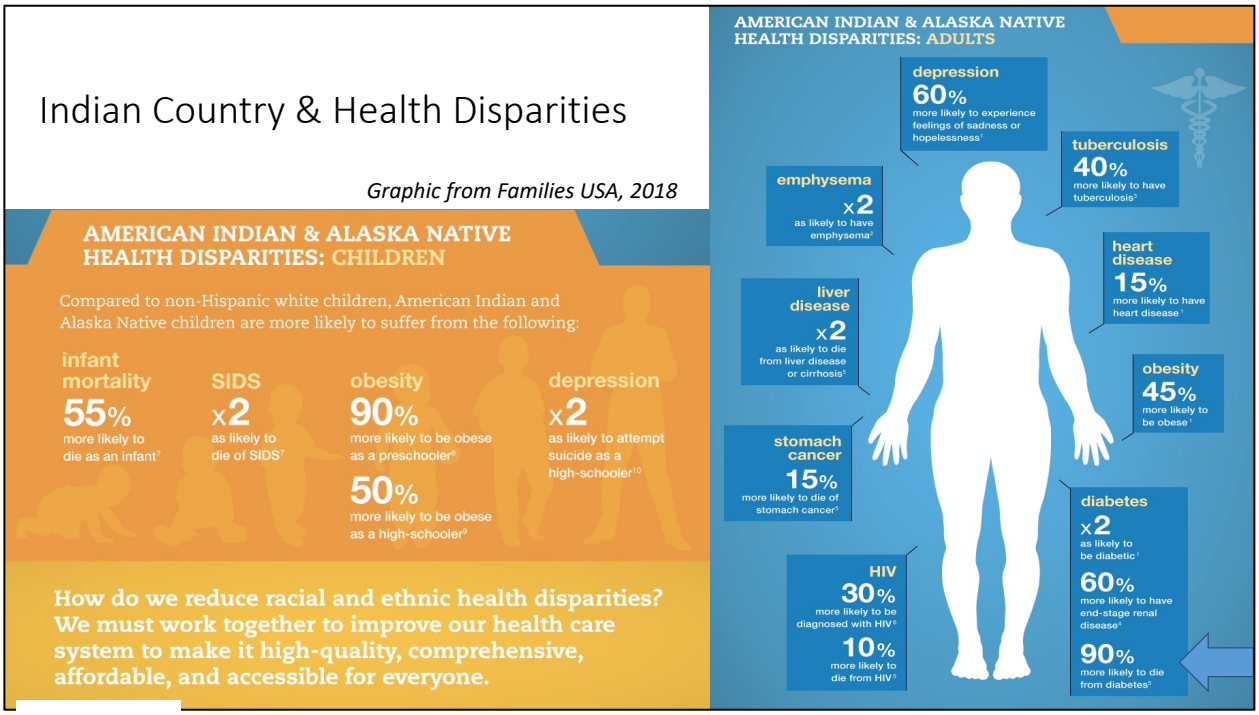
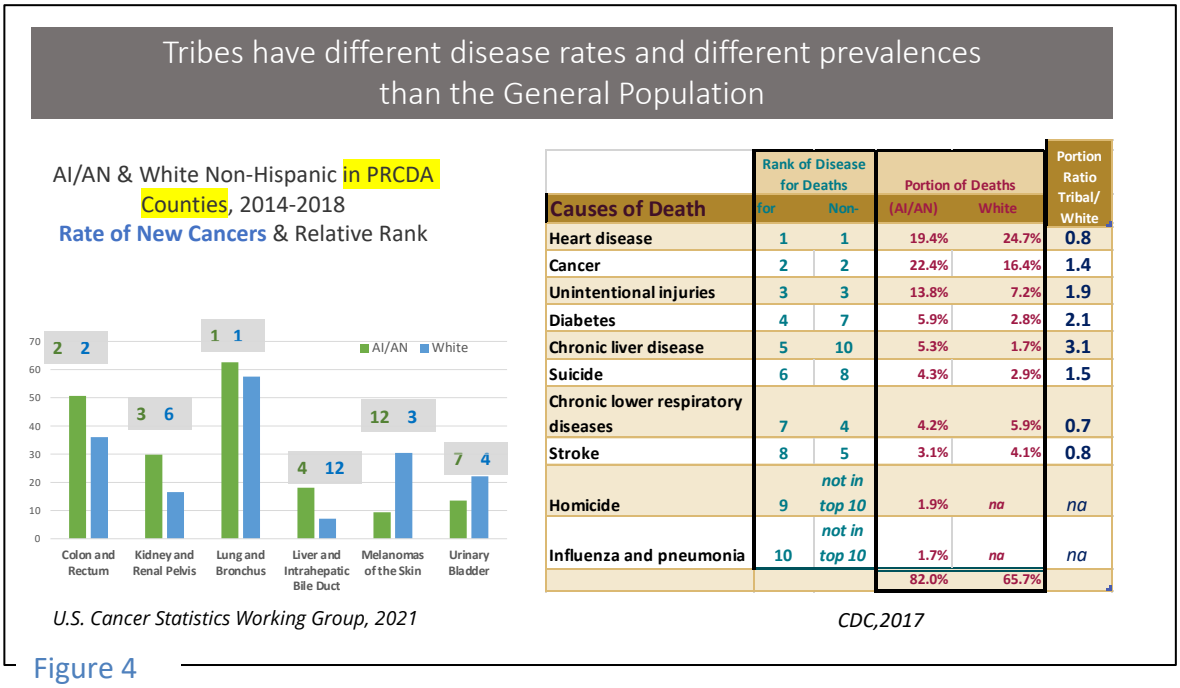


Figure 3



Causes of Death	Rank of Disease for Deaths for	Rank of Disease for Deaths Non-	Portion of Deaths (AI/AN)	Portion of Deaths White	Portion Ratio Tribal/ White
Heart disease	1	1	19.4%	24.7%	0.8
Cancer	2	2	22.4%	16.4%	1.4
Unintentional injuries	3	3	13.8%	7.2%	1.9
Diabetes	4	7	5.9%	2.8%	2.1
Chronic liver disease	5	10	5.3%	1.7%	3.1
Suicide	6	8	4.3%	2.9%	1.5
Chronic lower respiratory diseases	7	4	4.2%	5.9%	0.7
Stroke	8	5	3.1%	4.1%	0.8
Homicide	9	*not in top 10*	1.9%	*na*	*na*
Influenza and pneumonia	10	*not in top 10*	1.7%	*na*	*na*
			82.0%	65.7%	

CDC,2017

Figure 4

But it is the overall picture of tribal health that NTTC recommends consideration of in assigning an UFH. Poor health in general limits the body's ability to respond to disease. And about one-third of AI/AN adults (31.9%) had multiple chronic conditions, compared with about one-fourth of all U.S. adults (24.2%). AI/AN adults (20.6%) were more likely to be in fair or poor health than all U.S. adults (12.1%) (NCHS 2020). These health disparities are not inequalities, but rightly disparities because they are the result of systematic greater social or economic obstacles to health historically linked to discrimination or exclusion, meaning that it will take generations to redress them. Tribal peoples represent six and one-half million American citizens whose health and environment the USEPA's mission and trust responsibility it is to protect.

Biological susceptibility is not only a result of underlying disease status, but of other intrinsic factors such as life stage, genetics, and nutrition, and extrinsic factors such as social and life circumstances, like poverty and chronic life stress (Koman et al 2019). The US HHS recognizes 5 broad community-based social circumstances that help to determine community health, and tribes have disparities in every category. Poverty is associated with a wide range of disease. According to the United States Census Bureau (2015), 28.3% of American Indians live in poverty, the highest rate among any other race. For additional examples of disparities in the social determinant of health, see Figure 5 below, with citations included in the graphic.

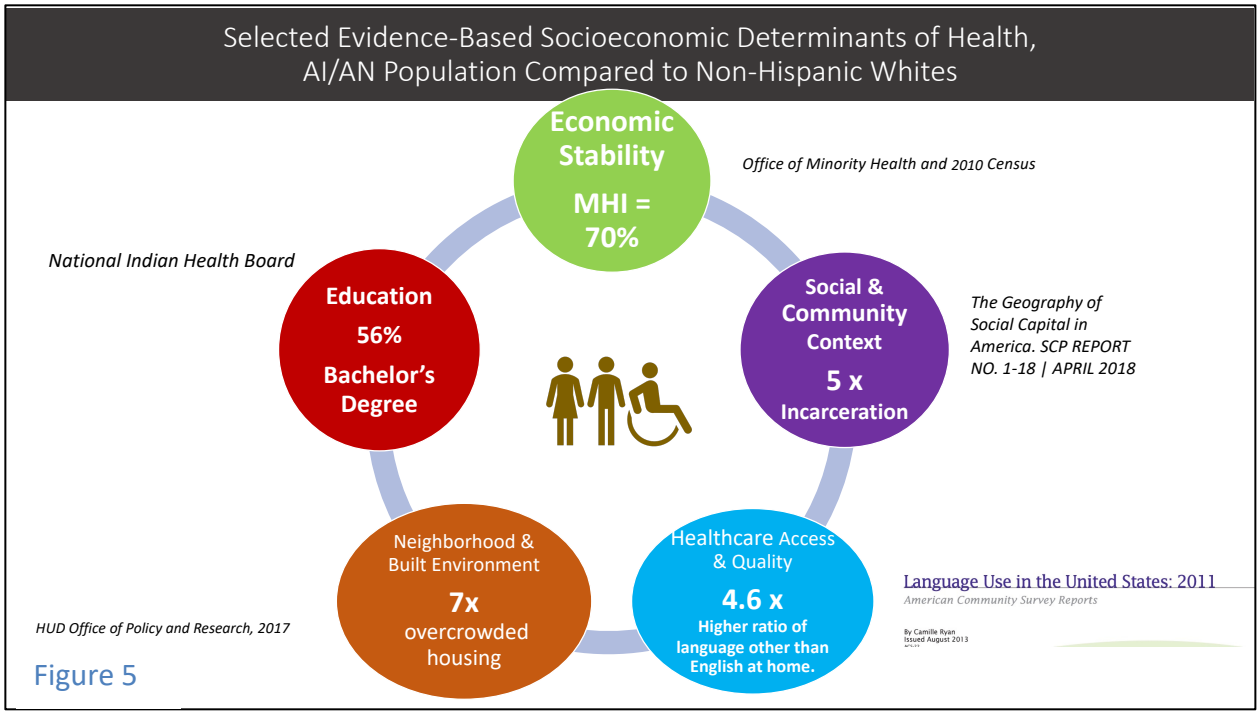


Figure 5

Groups that fare poorly in the SDOH have poorer health outcomes, and tribes are no exception. EPA therefore must incorporate the consideration of subpopulations with chronic disease and who face multiple poor social determinants of health linked to poor disease outcomes into their UFH factor. The systemic nature of disparities in health outcomes for tribes partly resides in the health care system. Access to hospitals in many tribal communities is limited and for the 40% of Alaska tribes, it is a plane ride away for non-Intensive Care. In 2017, IHS spent $3,332 per person, compared with $9,207 spent per capita by the U.S. health care system overall. This lack of funding results in staffing that is 20 % lower than what the IHS recommends (Shah 2020).

One reason for a poorer biological response to a chemical lies in the science of Allostatic load, which is

> the cost of chronic exposure to fluctuating or heightened neural and neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful (Guidi et al. 2021).

Allostatic overload can develop from exposure to frequent stressors that physiologically tax the ability of an individual to recover (Guidi et al 2021). The implication for poorer biological response outcomes is clear as multiple systems become impaired that are critical to efficient elimination and mitigation of effects. Brain architecture and neurochemical functions are affected by both genomic and nongenomic mechanisms, adjustments in the immune system (e.g., leukocytes, cytokines, inflammation) occur, with immunosuppressive effects in the long run and alteration in body functions involving cardiovascular and gastrointestinal systems, endocrine-metabolic balances and sleep may ensue, all critical to the body's chemical response.

In examining immunosuppressive effects from PFBA, a population burdened with allostatic overload that already is overburdened with immunosuppression could be expected to respond at lower dose levels and thus be at greater risk for development of disease. As the IRIS review points out, the potential for immunotoxicity represents an area of concern across several constituents of the larger PFAS family (primarily long-chain PFAS) (5-17). EPA states no studies have evaluated these outcomes following PFBA exposure or following exposure to the structurally related PFBS described above. No chemical-specific information is available to judge the degree to which the existing endpoints in the PFBA Toxicological Review would be protective of immunotoxicity. This deficit rightly is part of the justification for assigning an uncertainty factor greater than 1 for the UF_D, although as NTTC has pointed out, we believe an UF_D of 10x should be adopted. However, the additional issue of immunotoxic effects on already immunosuppressed populations was not addressed, and this deficit rightly belongs in the UF_H.

A large body of literature exists on the history of a people since colonialism and it documents a disproportionate allostatic burden on tribal peoples. A recent Washington Post article describing the effect of COVID-19 on individual members and their tribes discusses in detail the impact of losing family members on a people who already have a heavy disproportionate burden of loss of family members through the above-mentioned health disparities, a concept studied by Umberson (2017) who coined the phrase 'gap of grief''. Bereavement has its own adverse health consequences and when placed on top of additional socioeconomic disparities produces a 'weathering' of both physical and mental health. Unfortunately for tribal peoples, their children experience death and loss and multiple childhood traumas at substantially greater rates than non-Hispanic whites or other ethnicities. One in 168 AI/AN children have lost a parent to Covid, compared with 1 in 753 for white children.

NTTC realizes that the science of incorporating chronic and acute health impairment considerations into a reference dose derivation is new and simply states that a UFH that accommodates these considerations for susceptible sub populations versus the general population, should be assigned, and an additional 10 X factor as is standard in this field should be employed.

Seriousness of effect

As we mentioned earlier, IRIS could do a better job of trying to understand what developmental effects might mean to susceptible subpopulations. Tribal children, who are disproportionately burdened with higher allostatic load and

functional impairment and depression from acute events such as COVID-19 loss, which reduce their body's coping mechanisms in experiencing trauma, are also already disproportionately burdened with Adverse Childhood Experiences (ACE). It is well established that ACE results in development delays and impacts brain development in children under six (Bhushan et al 2020). Giano et al (2021) found that the average ACE score (number of childhood traumas experienced) for AI/AN participants was 2.32, approximately 40% higher than for individuals who identify as Black (1.66) or Hispanic (1.63) and over 50% higher than for individuals who identify as White (1.53).

NTTC strongly asserts that a difference in the seriousness of the developmental delay effects associated with PFBA likely exists between tribes as a susceptible subpopulation and the general population. And that difference is not accounted for in the Review, which notes that "the evidence indicates PFBA exposure is likely to cause adverse development effects in humans (Table 3-10)." The interdependence of age, genes and environment shapes developmental trajectories (Levy 2018) so that tribal children are at a disadvantage if burdened with developmental delays, which are associated with PFBA.

Developmentally delayed children can exhibit lower IQs and more errors in copy and memory tasks when compared to typically developed children (Piccolo et al 2016). A poor start in school is a predictor of high school dropout (Hickman et al 2008), which in turn is associated with low income, poverty, incarceration, and suicide, all of which are disproportionately experienced in tribal populations (Gregory et al. 2008). Developmental effects for tribal peoples thus arguably have more serious outcomes, helping to perpetuate systematic health disparities. While the overall impact of potential developmental effects on tribal populations is uncertain and may be small, it may also be large. It is NTTC's comment that, in line with EPA risk assessment forum guidance for factors to be considered for susceptible subpopulations, the seriousness of developmental effects is different and should be incorporated into a higher UF_H.

In discussing the seriousness of the effect, NTTC would be remiss in not remarking upon the seriousness of losing tribal elders as a potential outcome of increased incidence or severity of liver disease that may be associated with exposure to PFBA. Beyond the 60% greater risk of chronic liver disease diagnosis as compared to non-Hispanic whites, according to the HHS Office of Minority Health, the overall death rate in 2018 for American Indians/Alaska Natives **was almost four times** higher than the non-Hispanic white population. This very difficult fact relates to a greater seriousness of the hepatic effects overall for the tribal population versus the general population. Beyond that, the loss of a single tribal elder has a substantially greater impact on the tribal population than does the loss of a senior citizen on the general population. Tribes are distinct populations within the larger tribal population. Each has its own culture upon which Socio-cultural wellbeing depends. While the loss of one in 100,000 persons affects the family and friends of that one 'Strawman' individual, if that person is a tribal elder, it will have a lasting impact on an entire nation. NTTC recommends reading a recent NY Times article that documents this phenomenon using ethnographic observation (Healy 2021).

NTTC realizes that the science of incorporating epigenetics, allostatic load, developmental outcomes, and other germane fields is new. A lack of data makes such incorporation for susceptible subpopulations even more uncertain. NTTC again states that an increase in UFH factor for this and all IRIS chemical reviews is a reasonable approach until risk assessment science catches up with these important fields that are critical to human health.

Latency of effect

It is important to realize that chronic exposure truly may be lifetime exposure for tribal peoples, and many who live in and near tribal lands live their whole lives there. Duration of exposure is very high because they eat from local

wild food, drink from local water, recreate locally, catch and prepare food locally, work locally, etc., and a different response timing may result. Only subchronic effect studies were noted, and NTTC is concerned that longer studies might have demonstrated different or greater effects.

Additionally, it should be noted that the above discussion of developmental effects and their outcomes in later life pertains to a different latency for those effects. Indeed, developmental effects can result in epigenetic effects to affect future generations, and epigenetic effects are less modulated with populations that experience heavy allostatic load, as they are more likely to have structural changes in their stress response (termed toxic stress response) making them more susceptible to toxins. Multiple studies indicate a higher propensity for epigenetic effect for individuals with high allostatic load. Latency of effect indeed must be studied not chronically but cross generation.

Finally, the effect of chemical mixtures on response lag time is unclear, and the effect on susceptible subpopulations with multiple organ stressors is even less clear. This fact alone should give rise to an additional 10X in the UFH. Tribes are fenceline communities. Tribal peoples, from infants to elders, are out in the natural environment for longer periods and more diverse activities that other groups. Because wastewater and waste disposal facilities are generally managed locally in tribal and rural areas, tribes are also likely to conduct lifeways in and around both facilities, both of which clearly release chemical mixtures and to which tribes will be exposed.

The discussion of mixture consideration is beyond the scope of NTTC staff resources at this time, but NTTC comments that it is of high concern regardless and asks for a discussion with IRIS staff on this issue at a later date.

Conclusion

The hazard values derived by IRIS are in general critical to tribal peoples because currently their exposures to chemicals found in natural environments, and those associated with indoor air quality, are missing or under-represented in EPA risk assessments, such as those conducted under TSCA. The absence of an inhalation reference concentration is troubling to this Council as it may exacerbate the underrepresentation of tribal lifeways and exposures in TSCA evaluation. We recommend both a more detailed consideration of the inhalation pathway and route to route derivation of an inhalation RfC employing appropriate uncertainty factors..

The derived oral chronic reference dose, as well as the acute, subchronic, and system-specific reference doses, do not adequately protect tribes with any reasonable certainty. By analyzing the evolution of uncertainty factors from a historical perspective, Martin et al 2013 found that the default uncertainty factors are intended to represent adequate rather than worst-case scenarios. As described above, Tribal peoples will be disproportionately represented in worst case scenarios, meaning that unless the reference dose is lowered to reflect the greater uncertainty inherent in effects on the tribal susceptible subpopulation, tribes will once again be under-protected.

Should you or your staff have questions or comments regarding our letter, please contact myself, Dianne Barton, NTTC Chair, at (503) 731-1259 / bard@critfc.org or Susan Hanson, NTTC Co-Chair, at susanthanson9@icloud.com.

We look forward to further discussion on the issue of reference dose derivation for the tribal susceptible subpopulation, and request your office reach out to us within 3 months of this date.

Sincerely,

Dianne C. Barton, Ph.D.
Chair, National Tribal Toxics Council

REFERENCES

Alaska Department of Environmental Conservation (ADEC), Water Quality Standards, Assessment and Restoration Program, https://awqms2.goldsystems.com/Login.aspx?userLoginName=AKPUBLIC&dataAnalysisCriteriaSetUid=1198, accessed Nov 5, 2021.

Bhushan D, Kotz K, McCall J, Wirtz S, Gilgoff R, Dube SR, Powers C, Olson-Morgan J, Galeste M, Patterson K, Harris L, Mills A, Bethell C, Burke Harris N, Office of the California Surgeon General. Roadmap for Resilience: The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health. Office of the California Surgeon General, 2020. DOI: 10.48019/PEAM8812.

CDC, Leading Causes of Death - Males - Non-Hispanic American Indian or Alaska Native - United States, 2017

Farrigan, Tracey Racial and Ethnic Disparities in Educational Attainment Persist in Rural America, Finding: Employment & Education USDA Economic Research Service, November 02, 2020

Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance--United States, 1999-2011. Chest. 2013;144(1):284-305. doi:10.1378/chest.13-0809.

Giano, Zachary & Wheeler, Denna & Hubach, Randolph. (2020). The frequencies and disparities of adverse childhood experiences in the U.S. BMC public health. 20. 1327. 10.1186/s12889-020-09411-z.

Grandjean P, Timmermann CAG, Kruse M, et al. Severity of COVID-19 at elevated exposure to perfluorinated alkylates. Preprint. medRxiv. 2020;2020.10.22.20217562. Published 2020 Oct 26. doi:10.1101/2020.10.22.20217562

Gregory P. Hickman, Mitchell Bartholomew, Jennifer Mathwig & Randy S. Heinrich (2008) Differential Developmental Pathways of High School Dropouts and Graduates, The Journal of Educational Research, 102:1, 3-14, DOI: 10.3200/JOER.102.1.3-14

Guidi J, Lucente M, Sonino N, Fava G, A: Allostatic Load and Its Impact on Health: A Systematic Review. Psychother Psychosom 2021;90:11-27. doi: 10.1159/000510696

Healy, Jack Jan. 13, 2021, Section A, Page 6 of the New York edition with the headline: Cultural Crisis for American Indians as Elders Die. Laffey, K.G., Nelson, A.D., Laffey, M.J. et al. Chronic respiratory disease disparity between American Indian/Alaska Native and white populations, 2011–2018. BMC Public Health 21, 1466 (2021). https://doi.org/10.1186/s12889-021-11528-8

Levy Y. 'Developmental Delay' Reconsidered: The Critical Role of Age-Dependent, Co-variant Development. Front Psychol. 2018;9:503. Published 2018 Apr 23. doi:10.3389/fpsyg.2018.00503

McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev. 2014;47:578-591. doi:10.1016/j.neubiorev.2014.10.012

Health and Human Services, Office of Minority health https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=32#1 , access Nov 5, 2021.

JHU.edu, Johns Hopkins Center for American Indian Health, https://hub.jhu.edu/2021/10/11/map-covid-19-impact-american-indian-population/ access November 5, 2021.

Koman PD, Singla V, Lam J, Woodruff TJ (2019) Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. PLOS Biology 17(8): e3000372. https://doi.org/10.1371/journal.pbio.3000372

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000372

Perez F, M. Nadal, A. NavarroOrtega, F. Fàbrega, J.L. Domingo, D. Barceló, M. Farré Accumulation of perfluoroalkyl substances in human tissuesEnviron. Int., 59 (2013), pp. 354-362, 10.1016/j.envint.2013.06.004

National Center for Health Statistics (NCHS) provisional death counts (data through August 14, 2021). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

Pachkowski B, Post GB, Stern AH. The derivation of a Reference Dose (RfD) for perfluorooctane sulfonate (PFOS) based on immune suppression. Environ Res. 2019 Apr;171:452-469. doi: 10.1016/j.envres.2018.08.004. Epub 2018 Aug 8. PMID: 30739020.

Piccolo, L.d., Segabinazi, J.D., Falceto, O.G. et al. Developmental delay in early childhood is associated with visual-constructive skills at school age in a Brazilian cohort. Psicol. Refl. Crít. 29, 41 (2016). https://doi.org/10.1186/s41155-016-0048-2

Shanshan Liu, Shiyi Zhao, Zhihong Liang, Fei Wang, Feiyun Sun, Da Chen Perfluoroalkyl substances (PFASs) in leachate, fly ash, and bottom ash from waste incineration plants: Implications for the environmental release of PFAS Science of The Total Environment, Volume 795, November 2021

Umberson, Julie Skalamera Olson, Robert Crosnoe, Hui Liu, Tetyana Pudrovska,

Rachel Donnelly Race differences in death of family members, Proceedings of the National Academy of Sciences Jan 2017, 114 (5) 915-920; DOI: 10.1073/pnas.1605599114

Pindus, Nancy Kingsley, G. Thomas Biess, Jennifer Levy, Diane Simington, Jasmine Hayes, Christopher Urban InstituteHUD Office of Policy and Research. Housing Needs of American Indians and Alaska Natives in Tribal Areas: A Report From the Assessment of American Indian, Alaska Native, and Native Hawaiian Housing Needs. Authors January 2017

U.S. Census American Housing Survey 2019

Shanshan Liu, Shiyi Zhao, Zhihong Liang, Fei Wang, Feiyun Sun, Da Chen Perfluoroalkyl substances (PFASs) in leachate, fly ash, and bottom ash from waste incineration plants: Implications for the environmental release of PFAS Science of The Total Environment, Volume 795, November 2021

Shah , Armav et al., "The Challenge of COVID-19 and American Indian Health," To the Point (blog), Commonwealth Fund, Aug. 12, 2020. https://doi.org/10.26099/m5ww-xa13

Villarroel MA, Clarke TC, Norris T. Health of American Indian and Alaska Native adults, by urbanization level: United States, 2014–2018. NCHS Data Brief, no 372. Hyattsville, MD: National Center for Health Statistics. 2020.

Wang G, Wu L. Healthy People 2020: Social Determinants of Cigarette Smoking and Electronic Cigarette Smoking among Youth in the United States 2010-2018. Int J Environ Res Public Health. 2020;17(20):7503. Published 2020 Oct 15. doi:10.3390/ijerph1720750