

Briefing Report

**Review of the Toxicological Profile for Perfluoroalkyls,
Draft for Public Comment, June 2018**

**Agency for Toxic Substances and Disease Registry (ATSDR)
U.S. Department of Health and Human Services**

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Introduction

This briefing report was prepared at the request of the New Hampshire Department of Environmental Services (NHDES) and provides information on specific topics identified by the Department. Much of the information in this briefing was obtained from review of the public comment draft report, *Toxicological Profile for Perfluoroalkyls* prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) released in June 2018. Other information for the briefing was obtained from recent U.S. EPA, National Toxicology Program (U.S. Dept. of Health and Human Services), and Interstate Technology and Regulatory Council (ITRC) reports, as well as recent literature. The briefing was originally tasked to focus on perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), but was later expanded to include perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA). The opinions expressed in this report are solely those of the author.

The report is organized by topic, as follows.

1. Differences between the studies/information considered in the ATSDR Profile and those used by the USEPA to develop their 2016 PFOS/PFOA Health Advisories.

The toxicological analyses underpinning the USEPA oral reference doses (RfDs) for PFOA and PFOS are presented in documents dated May 2016 (*Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, EPA Document Number 822-R-16-003; and *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)*, EPA Document Number 822-R-16-002). The ATSDR Toxicological Profile is based upon literature searches, the last of which was conducted in May 2016 according to Appendix B of the profile. However, this report, published in 2018, contains references as recent as 2018.

Despite the short interval between these USEPA and ATSDR reports, a number of studies were published during this period and were considered for the ATSDR but not the USEPA analysis. Probably the most important of these are:

a. Thirteen epidemiological studies cited by ATSDR but not USEPA. Several of these provide evidence of an association between PFOA and/or PFOS and altered immune function. Although epidemiology studies were not used directly in deriving the MRLs, these studies support the case that adverse immune system effects observed in animals are relevant to humans. This may have contributed to different opinions regarding the strength of evidence regarding potential immunotoxicity of PFOA and PFOS by ATSDR and USEPA.

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b. Koskela et al., Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. *Toxicol. Appl. Pharmacol.* 301:14-21, 2016. This paper provides data on bone development in mice previously tested for neurobehavioral effects (Onishchenko et al., 2011). Had the USEPA been able to review this study, they might have accepted it [as ATSDR did] as providing a somewhat lower LOAEL for PFOA, even though only one dose was tested. Generally, studies employing only one dose are not suitable for conducting dose-response analysis, and in fact the USEPA rejected the Onishchenko study for dose-response analysis for that reason. However, the Koskela et al. 2016 and Lau et al. 2006 studies looked at some of the same endpoints in mice, and when the data are considered together could be considered to demonstrate that the LOAEL should be 0.3 mg/kg/day (chosen by ATSDR) instead of 1 mg/kg/day (chosen by the USEPA).

2. The specific health effects/endpoints upon which ATSDR’s Minimal Risk Level (MRLs) are based, compared with those cited by USEPA in their 2016 HAs.

	USEPA		ATSDR	
	Study	Endpoint	Study	Endpoint
PFOA	Lau et al. 2006	Reduced ossification of phalanges and accelerated puberty in mice	Onishchenko et al. 2011 Koskela et al. 2016	Neurodevelopmental and skeletal effects in mice
PFOS	Luebker et al. 2005 (two-gen study)	Reduced rat pup weight	Luebker et al. 2005 (two-gen study)	Delayed eye opening and decreased rat pup weight

Candidate Adverse Effects

Various candidate endpoints were considered by both the ATSDR and USEPA, as well as by states when developing their own risk-based criteria for PFOA and PFOS. There is a rationale for inclusion of each of these endpoints, but all have weaknesses. The absence of a clear choice for the best endpoint to use has led to various agencies selecting different endpoints in deriving PFOA and PFOS toxicity values (see Table 5.1 in ITRC, 2018). The following is a brief summary of some of the more important candidate endpoints.

PFOA – skeletal alterations in offspring. Both USEPA and ATSDR accepted skeletal alterations in the offspring of PFOA-treated mice as a relevant adverse effect, and it was considered a critical effect in the derivation of both the USEPA RfD and the ATSDR MRL for PFOA (see table above). The EPA selected Lau et al. (2006) as the critical study, which showed reduced ossification of phalanges in pups. The ATSDR based their intermediate duration MRL in part on altered long bone morphology and decreased bone mineral density observed in pups from mice exposed to PFOA (Koskela et al., 2016). Some have criticized these skeletal alterations as being of unclear consequence (no impairment of function or lasting effect) and human relevance.

PFOA – neurodevelopmental defects. This is cited as a critical effect by ATSDR (along with skeletal effects, see table above). Altered behavior was observed in offspring of PFOA treated dams. A recent study (Goulding et al., 2017) also found increased activity in male offspring, but at a higher dose (1 mg/kg/day LOAEL and 0.3 mg/kg/day NOAEL versus 0.3 mg/kg/day LOAEL in the Onishchenko et al. 2011 study.)

PFOA – delayed mammary gland development. Although this effect occurred in mice at doses below the LOAEL for skeletal and neurobehavioral effects, it was rejected by both USEPA and ATSDR because the mode of action is not known and for lack of functional consequence – no impairment of lactation was observed and offspring were not malnourished. Some have argued that the endpoints chosen by USEPA and ATSDR also did not have a known mode of action or clear functional consequence, and that delayed mammary gland development is relevant in determining a RfD/MRL for PFOA. New Jersey calculated a candidate RfD based upon delayed mammary gland development, but did not use it as the

primary basis for their recommended RfD. Instead, it was used as justification for applying an additional UF of 10 to an RfD calculated based upon increased liver weight.

PFOA – adverse effects on liver. This was selected as a critical effect in primates in a previous ATSDR draft, and effects have also been observed in mice and rats. It was not selected as a critical effect for PFOA in the current ATSDR draft or by the USEPA. An issue in interpreting liver effects is distinguishing between adaptive and adverse liver effects and whether a PPAR alpha mechanism is responsible, which raises the question of human relevance. Additionally, the USEPA and ATSDR both concluded that other effects of PFOA occurred at lower doses. New Jersey determined that liver effects are relevant to humans and used a different study (Loveless et al., 2006) to model the dose-response relationship for PFOA effects on liver. They concluded that liver effects occur at doses as low or lower than other effects [except for effects on mammary gland development] and used increased liver weight as the primary basis for its PFOA RfD.

PFOS – reduced pup weight. This endpoint was considered to be a relevant adverse effect, and it was selected as a critical effect by both USEPA and ATSDR (see table above). Critics point out that the decrease in body weight was small, transient, and associated with a minimal increase in litter size (which could explain the smaller body weight), and the authors of the study did not consider the observation to be toxicologically significant.

PFOS – delayed eye opening in rat pups. This endpoint was considered relevant by ATSDR. Critics of this choice point out that the delay was slight (0.6 days compared to controls) and the authors of the study did not consider this an adverse outcome.

PFOS – immunotoxicity. The immunotoxicity studies in animals available to USEPA and ATSDR were the same, but the agencies reached different conclusions. The USEPA concluded that animal immunotoxicity studies were too inconsistent to use for dose-response assessment:

“The animal immunotoxicity studies support the association between PFOS and effects on the response to sheep red blood cells as foreign material and on the natural killer cell populations; however, the doses with effects are inconsistent across studies for comparable endpoints. When both males and females were evaluated, the males responded at a lower dose than the females. Because of these uncertainties, EPA did not quantitatively assess this endpoint.” (Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS), USEPA, 2016).

The ATSDR, in contrast, was willing to accept the animal study data, at least for an analysis that led them to conclude a MF of 10 was needed to protect from immunotoxic effects for PFOS, PFNA, and PFHxS.

The ATSDR evaluated four animal studies that found immunotoxic effects of PFOS. The dose-response relationships for these studies are summarized in the table below, adapted from the ATSDR Toxicological Profile.

Effect		Dose (mg/kg/day)	Reference
Impaired response to sRBC in mice exposed 60 days	NOAEL	0.0083	Dong et al. 2009
	LOAEL	0.083	
Impaired response to sRBC in mice exposed 60 days	NOAEL	0.0167	Dong et al. 2011
	LOAEL	0.083	
Decreased resistance to influenza virus in mice exposed 21 days	NOAEL	0.005	Guruge et al. 2009
	LOAEL	0.025	
Suppressed response to sRBC in mice exposed 28 days	NOAEL	0.00016	Peden-Adams et al. 2008
	LOAEL	0.00168	

Adapted from ATSDR 2018.

A candidate MRL was developed from the NOAEL from Dong et al. 2011 because it identified the highest NOAEL and had the longest exposure duration. Although the Peden-Adams study had the lowest LOAEL, it was not considered further because it is not supported by the other three studies. At the opposite extreme, a study by Qazi et al. (2010) found no effects on response to sRBC at plasma PFOS concentrations after 28 days almost 100-times the highest concentration reported to cause effects in the Peden-Adams study. These inconsistencies in dose-response relationships illustrate the challenge in developing an MRL using mouse immunotoxicity data.

Endpoints for Other PFAS

The ATSDR toxicological profile developed intermediate MRLs for two additional PFAS, PFHxS and PFNA, which were not addressed by USEPA. Candidate adverse effects for these PFAS include the following:

PFHxS – thyroid toxicity. Two studies are cited by ATSDR as showing thyroid follicular cell hypertrophy and hyperplasia in rats. ATSDR selected this endpoint as the basis for their PFHxS MRL. Recent studies (e.g., Ramhoj et al. 2018) confirm thyroid effects as sensitive indicators of PFHxS toxicity in rats.

PFHxS – adverse effects on liver. ATSDR noted increased liver weight and centrilobular hypertrophy in PFHxS-treated rats, with a LOAEL similar to that for thyroid effects. The liver effects were, however, not considered relevant to humans. This decision has been criticized citing evidence that not all liver effects of PFAS are PPAR-alpha mediated and therefore may be relevant to humans.

PFHxS – adverse effects on reproduction. A recent study (Chang et al., 2018) suggests that PFHxS may have adverse reproductive effects in mice in the form of decreased litter size. The authors of the study indicate that the toxicological significance of this finding is unclear.

PFNA – developmental toxicity. The ATSDR cites three studies (two in mice and one in rats) showing developmental toxicity from gestational exposure to PFNA. Endpoints affected included pup survival, decreases in birth weight, and developmental delays. The intermediate MRL is derived based from a study with the lowest LOAEL for developmental effects (based on time weighted average (TWA) serum concentration, 10.9 µg/mL). Wolf et al. (2010) also found developmental toxicity in wild-type mice at a somewhat higher PFNA dose (TWA 17.6 µg/mL), but no developmental toxicity when the same dose was given to PPAR-alpha knockout mice. This raises the issue of the relevance of this effect to humans.

PFNA – adverse effects on liver. PFNA has been shown to increase both maternal and fetal liver weights (NJDWQI 2018). As with liver effects from other PFAS, there is an issue whether these represent an adverse effect relevant to humans. A developmental toxicity study conducted in mice (Das et al., 2015) provided data on maternal liver weight changes that New Jersey considered a critical effect and used dose-response data for this effect to derive a reference dose for PFNA.

3. Known limitations of the studies that form the basis of ATSDR's draft MRLs and EPA RfDs

Study	Limitations/Weaknesses
Lau et al., 2016	<ul style="list-style-type: none"> • No NOAEL identified • Non-monotonic dose-response relationships for delayed ossification and accelerated puberty
Onishchenko et al, 2011	<ul style="list-style-type: none"> • Only one dose examined • Statistical analysis has been criticized and low number of animals • No data on possible maternal effects reported • No serum PFOA data reported
Koskela et al., 2016	<ul style="list-style-type: none"> • Only one dose examined • Results analyzed on per fetus basis rather than per litter basis. • Low number of animals • No data on possible maternal effects reported • No serum PFOA data reported
Luebker et al., 2005	<ul style="list-style-type: none"> • Effects observed were of questionable significance

4. Evaluation of gaps in data, limitations of studies included in ATSDR's draft MRLs, etc. where professional judgment is required to adjust/account for uncertainty in establishing the draft MRLs.

Selection of uncertainty factors

	USEPA		ATSDR	
	POD	UF	POD	UF/MF
PFOA	0.0053 mg/kg/day LOAEL	300 (10 UFH; 3 UFA; 10 UFL)	0.000821 mg/kg/day LOAEL	300 (10 UFH; 3 UFA; 10 UFL)
PFOS	0.00051 mg/kg/day NOAEL	30 (10 UFH; 3 UFA)	0.000515 mg/kg/day NOAEL	300 (10 UFH; 3 UFA; 10 MF) MF based on concern for immunotoxicity
PFHxS	ND	ND	0.0047 mg/kg/day NOAEL	300 (10 UFH; 3 UFA; 10 MF) MF based on concern for immunotoxicity
PFNA	ND	ND	0.001 mg/kg/day NOAEL	300 (10 UFH; 3 UFA; 10 MF) MF based on concern for immunotoxicity

POD – Point of departure (as human equivalent dose); UF – Uncertainty Factor; LOAEL - lowest observable adverse effect level; NOAEL – no observable adverse effect level; UFH – intraspecies variability; UFA – interspecies variability; UFL – LOAEL to NOAEL extrapolation; MF – modifying factor; ND – Not determined

The uncertainty factors selected by ATSDR and the USEPA follow standard established practice and guidance. As noted above, the UF values selected by the two agencies are the same, with the only difference being a MF of 10 applied to PFOS by ATSDR. The use of this modifying factor, while within ATSDR guidance, is unusual, and many have questioned why ATSDR did not instead base their MRL directly on immunotoxicity endpoints.

Because there is an element of professional judgment in the application of UFs (even with explicit guidance on their selection), it is not unusual for scientists to reach different conclusions, and a number of public commenters have recommended different choices. For example:

- UFH (intraspecies variability) – The choice of a UFH of 10 by ATSDR and USEPA is consistent with standard practice. Some commenters have questioned whether a full UF of 10 is required to address this uncertainty. Generally a default factor of 10 is used unless there is substantial information available regarding variability in sensitivity to the chemical among humans, and nothing specific along these lines has been offered.
- UFA (interspecies variability) – The default UFA is a factor of 10, which can be divided into two factors of 3 (log scale) — one for potential toxicokinetic differences between animals and humans and one for potential toxicodynamic differences. If potential toxicokinetic differences are addressed specifically and quantitatively, such as through toxicokinetic modeling, the first factor of 3 can be eliminated, leaving a factor of 3 for potential toxicodynamic differences. This is the case for both PFOA and PFOS by both ATSDR and USEPA. Some commenters have recommended that the second factor of 3 can be eliminated, contending it is unnecessary because rodent species are known to be more sensitive to these PFOA effects than humans. This argument appears to be based on an assumption that the effects are due to PPAR-alpha-related mechanisms to which humans are known to be less sensitive. While there is evidence that PPAR-alpha mechanisms are involved in *some* PFOA and PFOS effects, both USEPA and ATSDR have concluded that this evidence is insufficient to establish this as the only mechanism. [Note: The USEPA requires detailed evidence in order to conclude that an effect is attributed to PPAR-alpha mechanisms, and once established, the effect is considered not relevant to human risk assessment.]
- UFL (extrapolation from a LOAEL to NOAEL) — The default factor of 10 is routinely applied to the LOAEL when no NOAEL is available. The choice of both agencies to apply this in the case of PFOA, where the critical studies supplied only a LOAEL, is standard practice. New Jersey has questioned application of this factor given the non-monotonic dose response relationships for the critical effects of PFOA.

5. Challenges/limitations in translating the results of animal studies in establishing standards for humans, including any unique challenges for PFAS compounds.

The principal challenge in translating the results of animal studies in establishing standards for humans is uncertainty as to whether effects observed in animals are relevant to humans, both qualitatively and quantitatively. Generally, effects observed in animals are assumed to apply to humans as well unless there is convincing evidence otherwise, generally in the form of an established mechanism of toxicity that can be shown not to occur in humans. When epidemiological and animal studies both show evidence for the same effect for a chemical, this strengthens the case for human-relevance of the animal observations. An example for PFAS compounds is the diminished antibody response to an antigen challenge associated with

increasing PFOS serum concentrations in humans and with increasing PFOS dose in animals (although the concordance isn't perfect).

Unlike human studies, the exposures of animal subjects are carefully controlled and known with relative certainty. This is very important in establishing dose-response relationships, which are critical for risk-based standard setting. However, this leads to the second challenge in translating the results of animal studies for human standard setting — translating the dose-response relationships observed in animals to something applicable to humans. The dose required to produce an effect in humans can be the same, lower, or higher than the dose that produces toxicity in animals depending upon the toxicokinetics of the chemical (absorption, distribution, metabolism, and elimination), as well as potential differences in the sensitivity of target organs/tissues to the toxic effect of the chemical. Correcting for toxicokinetic differences among species is extremely important for PFAS because they have unusually large differences, especially between laboratory rodents and humans. Both the USEPA and ATSDR have attempted to address this problem through toxicokinetic modeling — using available information on the toxicokinetics of PFAS in laboratory animals and humans to estimate the blood concentrations in humans corresponding to the blood concentrations in animal studies at which effects did or did not occur. Differences in tissue sensitivity among species is also an issue for PFAS. Some have argued that the biochemical mechanism through which PFAS produce many of their effects is one to which humans are much less sensitive than laboratory rodents (PPAR- α). Other uncertainties in extrapolating the results from animal studies to humans are addressed through the application of specific uncertainty factors (UFs).

6. Other key areas/studies that ATSDR used to develop the draft MRLs that help explain differences between ATSDR MRLs and USEPA RfDs.

The manner in which doses from animal studies are extrapolated to equivalent human doses has a substantial influence on the MRL that is derived. Basic information needed for the extrapolation includes the plasma PFAS concentration at the NOAEL and/or LOAEL dose in the laboratory animal, the toxicokinetics of the PFAS substance in that species, strain, and gender, and the toxicokinetics of the PFAS substance in humans. The model of Wambaugh et al. (2013) was used by both USEPA and ATSDR for these extrapolations. For ATSDR's use of the model, it was migrated from R to MATLAB. Results of estimation of the average serum concentration produced from the same data by the two versions of the model found an average relative difference of 2.8% (range -6.6 to 13.5) (see page A-7 of the Appendix). There were also some differences between USEPA and ATSDR in the time weighted average concentration of the PFAS assigned to the same animal study and in the assumed half-life of the PFAS in humans (e.g., 839.5 days for PFOA by USEPA and 1400 days by ATSDR). Some commenters on the ATSDR profile argued that the half-life values assumed for humans are too conservative (i.e., too long), and that the extrapolation fails to take into account non-linear kinetics of PFAS.

In developing the intermediate MRL for PFOA and PFOS, the ATSDR limited consideration of candidate studies to those conducted in rodent strains for which PFOA or PFOS pharmacokinetic parameters were available in order to calculate a time weighted average (TWA) concentration corresponding to the various doses tested. For PFOA, this exclusion criterion did not result in the loss of many studies, but for PFOS several studies were excluded, including all four animal studies examining potential immunotoxicity. The same exclusion criteria were not applied in the development of MRLs for PFHxS and PFNA, however. For those PFAS, an approach involving estimation of the TWA concentrations based upon serum concentrations measured in the studies was considered sufficient. The same estimation approach was also considered adequate to assess the protectiveness of the of the candidate MRL for PFOS based

upon developmental toxicity. For this assessment, PFOS TWA serum concentrations were estimated from measured serum concentrations in the four immunotoxicity studies, and a candidate MRL based upon immunotoxicity was derived (3×10^{-6} mg/kg/day). This 10-fold lower candidate MRL was used as justification for applying a modifying factor of 10 to the developmental toxicity-based MRL to derive the final PFOS MRL 2×10^{-6} mg/kg/day). The inconsistent application of a requirement to have pharmacokinetic parameters for a PFAS in each species and strain contributing data on potential critical endpoints is not explained by ATSDR.

7. How an MRL relates a Maximum Contamination Level (MCL)

An MRL is developed by the ATSDR and “... is an estimate of the amount of a chemical a person can eat, drink, or breathe each day without a detectable risk to health.” (<https://www.atsdr.cdc.gov/minimalrisklevels/index.html>) MRLs are based on non-cancer effects. An MRL is intended for use as a screening level, meaning that it is used to determine whether the presence of a chemical might represent a health problem. Screening levels are set low so that there is high confidence that exposures at or below these levels are safe. An exposure above a screening level does not necessarily mean that adverse health effects will occur, but usually leads to further analysis to determine the risk from exposure. The ATSDR cautions [in bold print] that “**It is important to note that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies.**” (<https://www.atsdr.cdc.gov/mrls/index.asp>)

An MCL is a promulgated standard and sets a limit on the concentration of a chemical in drinking water. MCLs are intended to protect against adverse health effects taking into consideration anticipated exposures, as well as practical considerations such as technical feasibility and cost. The presence of a chemical above an MCL usually leads directly to some regulatory action.

8. How an MRL relates to a drinking water or groundwater standard

As noted above, the ATSDR does not develop MRLs to be used to set drinking water or groundwater standards. The MRLs are instead used to develop screening levels for ATSDR and other health professionals. To develop a screening level for drinking water or groundwater using an MRL, key decisions that need to be made including the following:

- a) What exposure pathways will be included? In addition to ingestion, will inhalation or dermal contact, such as during bathing, be addressed? Considerations include the need to address certain pathways due to chemical properties such as volatility, dermal absorption, etc., and also the importance of consistency with other drinking water or groundwater standards.
- b) Are there critical life stages that need to be protected? This decision is driven by the toxicity of the chemical and whether effects on life stages such as the fetus, infant, etc. pose a special risk. Consistency with the critical effect(s) on which the MRL is based is important. As a practical matter, if something other than a generic adult is selected as the relevant receptor on which the exposure assumptions are based, a follow-up decision must be made with regard to the sophistication that will be applied in determining the relationship between water concentration and dose for the sensitive life stage.

- c) What portion of the total allowed daily dose will be apportioned to drinking water and groundwater consumption (i.e., Relative Source Contribution)? Will a default value be applied (usually 20%), or will an analysis be conducted to derive a chemical-specific value based upon estimated exposures from other sources?

9. From a scientific standpoint, evaluation of the benefits/limitations of establishing a single standard for multiple PFAS, as VT, CT, and NJ have done.

Analyses of PFAS in blood of humans confirm what we already suspect, which is that exposures typically occur to a combination of PFAS rather than a single agent. A number of commenters on the ATSDR draft profile, as well as stakeholder input on the recent draft ITRC (Interstate Technology & Regulatory Council) PFAS guidance document, pointed out the limitation in trying to protect public health with a small number of standards for specific PFAS compounds, recommending that a chemical class-wide standard be developed. The availability of such a standard, if technically sound, would have obvious benefits in comprehensively addressing “real world” exposures to PFAS and in reassuring the public that nothing has been overlooked or left out of an assessment of PFAS risk on an individual or population basis.

The problem with this approach is that most of the information needed to construct a scientifically-defensible single standard is missing:

- a) We don't yet know which PFAS are most important from an exposure standpoint. Analytical methods are just now being developed to detect many of the PFAS and we don't yet know the full extent of ongoing PFAS exposures. Plus, the situation is dynamic, with some PFAS being phased out and new ones being introduced to commerce. Bottom line: We don't yet know the right suite of PFAS to include in our standard.
- b) Applying a single standard to a group of chemicals implies that we know something about the health effects they have in common and how they interact to produce those effects when exposure is to a combination of chemicals. We know something about the potential health effects produced by a handful of PFAS, a little about the potential health effects for perhaps a dozen more, and next to nothing for the others. Further, there is little understanding as yet about relative toxic potencies of specific PFAS, mechanisms of toxicity, and how PFAS might interact in combination (additive? inhibitory? synergistic?).

The National Institute for Public Health and the Environment in the Netherlands recently released a report describing a relative potency approach to assessing risk from a mixture of PFAS (RIVM, 2018). This report illustrates how this kind of approach could be used to calculate risks and set risk-based standards for PFAS as a class, but also illustrates the some of the problems doing so with the current state of knowledge. The relative potency approach for assessing the risk of toxicity of mixtures is based on the principle of dose-addition in which chemicals that produce the same toxic effect through the same mode of action are assumed to have additive effects. The concept is well accepted in risk assessment and is used, for example, in estimating risks and setting standards for mixtures of carcinogenic polycyclic aromatic hydrocarbons (PAHs) and carcinogenic polychlorinated dibenzo-p-dioxins and -furans (PCDDs, and PCDFs). In these examples, there is adequate evidence that the carcinogens within these mixtures have the same mode of action and the toxic effect being assessed (carcinogenicity) is one of primary concern.

The RIVM report develops toxic potency estimates for 11 PFAS with PFOA as the “index chemical” and using liver hypertrophy as the toxic endpoint. It demonstrates how concentrations of other PFAS can be converted to toxicologically equivalent concentrations of PFOA, and how the sum of these concentrations can be used for risk assessment and compared with PFOA regulatory standards. Although this represents a worthwhile exercise, there are at least three limitations in using this report as the basis for regulatory action of PFAS:

- a) While liver toxicity is arguably a sensitive endpoint, it may not be the endpoint of greatest concern. Further, as the report acknowledges, liver hypertrophy is not necessarily an indicator of adversity. It was chosen, seemingly in large part, because of the availability of data on hypertrophy for several PFAS. Some PFAS compounds appear to produce potentially adverse effects on developmental and immunotoxicity at lower doses, and a PFAS mixture assessment based upon liver toxicity, by itself, may not be adequate to meet health protection needs.
- b) The mode of action of many of the PFAS compounds on liver is not known. The report cites an EFSA (European Food Safety Authority) opinion on pesticides that a relative potency approach can be used for chemicals that have the same target but not necessarily the same mode of action. This opinion is not widely accepted in the U.S. however, and the absence of a common mode of action effectively precludes this approach according to EPA guidance.
- c) Although a step in the right direction, a mixture approach that addresses 11 PFAS is not likely to satisfy interest in developing an approach capable of dealing with the many PFAS to which exposure might occur.

There is considerable interest in gathering information needed for a more comprehensive approach to assessing risk to PFAS through new research as quickly as possible, but today it doesn't yet exist. Bottom line: Developing a single standard would require assumptions regarding toxicity of large numbers of PFAS for which there is little or no scientific support. Decisions of some agencies to apply a single standard to a collection of PFAS appears to be based primarily on a risk management approach that seeks to be precautionary (for example, Connecticut, see Ginsberg and Teal, 2016).

References

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