United States Environmental Protection Agency

Office of Water
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Contaminants to Monitor in Fish and Shellfish Advisory Programs: Compilation of Peer Review-Related Information

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Overview

State, Tribal, and territorial fish and shellfish advisory programs monitor and analyze fish and shellfish in waterbodies within their jurisdictions for contaminants. When contaminants occur in high enough concentrations to potentially affect the health of people eating fish and shellfish from those waters, the EPA recommends that those programs issue advisories regarding consumption to protect the consumers. To help state, Tribal, and territorial fish and shellfish advisory programs, the EPA recommends a set of contaminants to monitor in its *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories*.

The EPA is updating its fish advisory guidance for states, which was last revised in 2000. As part of that update, the EPA is adding to its list of contaminants found to accumulate in fish at levels that could be problematic for human health. The EPA did not investigate whether any contaminants on the existing list need to be removed. The process the EPA followed included the following activities:

- Performed an extensive literature search for published journal articles using a set of specified search terms.
- Compiled concentrations in fish and shellfish from articles and toxicity information from U.S. government sources.
- Calculated if the concentrations in fish and shellfish would exceed thresholds for safely eating 8 ounces per week for people who could become pregnant and the general population or eating 5 ounces per day for frequent consumers of seafood.
- Compiled two lists of contaminants that have been found in fish and shellfish at concentrations that may be of concern for human health – one list has toxicity information, allowing fish advisory consumption rates to be calculated, and the other list contains contaminants that do not have maximum allowable exposure information but the levels found in fish and shellfish are high enough to warrant monitoring.

The EPA then submitted the process and results (included in Appendix 1) to subject matter experts in toxicology and human health risk assessment for an independent, external peer review. The peer reviewers responded to the charge questions and had some suggestions, which a contractor compiled into a report (included in Appendix 2). The EPA considered these suggestions and made some changes to the process and the resulting list of contaminants.

This document is arranged in the following manner.

- Section 1 contains a summary of the process that was provided to the peer reviewers.
- Section 2 contains the main areas of suggestions from the peer review report.
- Section 3 groups the comments into areas and described the changes that were made to the process and list of contaminants in response to the peer reviewers' comments.
- Section 4 contains the final lists of contaminants that the EPA is recommending fish and shellfish advisory programs monitor.
- Appendix 1 contains the document provided to the peer reviewers.
- Appendix 2 contains the entire peer review report.

Section 1: Summary of Process

The EPA initiated a systematic screening process to identify any additional relevant compounds that are not currently included in the current version of its *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* (2000 Guidance). The EPA developed a protocol to compile peer-reviewed articles that provide a basis for choosing any new analytes. This section contains a summary of the process; the more detailed version that was sent to the peer reviewers is in Appendix 1.

Literature Review

Several environmental science, health, and toxicology databases were searched for relevant peer-reviewed publications using keywords and inclusion and exclusion criteria. The screening criteria for selecting publications identified before beginning the literature review included criteria in areas such as publication status, publication date, language, seafood species, and compounds analyzed. The EPA included only articles that were peer-reviewed, published in 2000 or later (to capture information published after the 2000 Guidance), and written in English.

The EPA searched the PubMed, PubChem, Web of Science, Environmental Science and Pollution Management, Science Direct, and Toxline databases for relevant articles. The EPA also utilized an internal literature search that had been conducted for harmful algal blooms (HABs) and HAB toxins.

Specific keywords were used to search the literature; some examples are included here, listed by category.

- Target analytes: PCBs OR contaminant OR constituent OR contamination OR emerging contaminant OR aquatic contaminant OR chemicals OR pollutants OR metals OR pesticides.
- Aquatic animal types: Finfish OR fish OR freshwater turtles OR shellfish OR bivalves OR crustaceans OR mollusks AND [edible tissue OR muscle tissue].

These efforts resulted in a compilation of more than 600 articles for further review. The EPA screened the articles collected during the literature search, and examined articles that had information in at least two of these areas: contaminant concentration levels in fish or shellfish, BCF or BAF data, oral toxicity data, and species found in the U.S.

From these articles, the EPA developed a preliminary list of 242 potential contaminants in the following classes:

- Antibacterial, antibiotic, and antimicrobial compounds.
- Brominated compounds.
- Chlorinated compounds.
- Cyanotoxins and neurotoxins.
- Flame retardants.
- Hormones.
- Industrial byproducts.
- Inorganics.
- Metabolites.
- Metals.
- Organophosphorus esters.
- Nanoparticles.
- Personal care products.
- Pesticides.
- Per- and polyfluoroalkyl substances (PFAS).
- Pharmaceuticals.
- Phthalates.
- Polychlorinated biphenyls (PCBs).
- Polychlorinated naphthalenes.
- Polycyclic aromatic hydrocarbons.
- Sulfonamides.
- Other.

The EPA then extracted concentration data from the articles, sorted them based on what parts were analyzed (e.g., fillet, whole body, organs), and removed any that were from species not found in U.S. waters or that were not measuring ambient conditions (e.g., lab dosing studies).[1]

The EPA refined the list of potential new contaminants by removing compounds without concentration data, compounds already on the monitoring list in the 2000 Guidance, and mixtures (e.g., BDE-119 + BDE-120, sum of PFAS), and this resulted in lists of 49 potential contaminants with fillet data, 55 with whole fish data, and 14 with shellfish data.

Consistent with its approach to developing water quality criteria, the EPA searched for toxicology information (e.g., reference dose, minimal risk level, cancer slope factor) for each of the contaminants on the list in the following eight peer-reviewed, publicly available sources:

1. EPA's Integrated Risk Information System (IRIS) program.
2. EPA's Office of Pesticide Programs Pesticide Chemical Search.
3. EPA's Office of Pollution Prevention and Toxics Existing Chemicals.
4. EPA's Office of Water Water Topics.
5. EPA's Office of Solid Waste and Emergency Response Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV).
6. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) Toxic Substances Portal.
7. Health Canada.
8. California Environmental Protection Agency's Office of Environmental Health Hazard Assessment - All Public Health Goals.

For PFAS compounds, the EPA used the reference doses and minimal risk levels for perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) and the PPRTV for perfluorobutane sulfonic acid (PFBS) that were used in the proposed national primary drinking water regulation released on March 14, 2023, and the reference doses in IRIS for perfluorobutanoic acid (PFBA), perfluorodecanoic acid (PFDA), and perfluorohexanoic acid (PFHxA).

Analyses

For each contaminant with a non-cancer toxicity value, the EPA calculated a non-cancer screening value using this equation from the 2000 Guidance:

$$\text{Non-cancer screening level} = \frac{\text{reference dose} \times \text{consumer body weight}}{\text{consumption rate}}$$

where:

Body weight of adult in general population and of frequent fish consumer = 80 kg
Body weight of pregnant person = 75 kg

[1] Fish and shellfish advisory programs are concerned with real-world conditions that reflect what is in the environment, whereas lab studies can be designed to determine what is possible to occur (e.g., amount of bioaccumulation), so the EPA used only articles that demonstrated contaminant accumulation in fish and shellfish in ambient waters.

Consumption rate of adult in general population and pregnant person = 8 oz/week * 28.35 g/oz * 1 week/7d = 32.4 g/d[2]
Consumption rate of frequent fish consumer = 142 g/d[3]

The non-cancer screening levels were compared to the concentration data extracted from the scientific literature.

EPA analyzed whether the maximum or average concentrations extracted from articles exceeded the non-cancer screening level for:

- An adult in the general population.
- A pregnant person.
- A frequent fish consumer.

EPA also calculated whether the maximum concentration and average concentration were within 75 percent of the non-cancer screening level for an adult in the general population to see if there were compounds that could be problematic but not currently accumulating to problematic levels. The EPA did not find additional compounds to include as a result of those analyses.

A contaminant's presence in fish does not necessarily indicate a human health risk exists. For the contaminants *without* non-cancer toxicity values, before the peer review, the EPA calculated a generic screening level to capture contaminants with fish tissue concentrations high enough to potentially be a human health concern after reference doses are developed. In its screening level calculations, the EPA used the lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed) available among the contaminants found in fish. The lowest toxicity value for compounds that were considered for inclusion on the monitoring list in this evaluation was 3×10^{-6} mg/kg-d, which was the minimal risk level for PFNA. The calculated generic screening level was 7.41×10^{-3} µg/g, which was compared to the maximum and average concentration data for each compound without toxicity values. After the peer review, a revised generic screening level was calculated for each class of contaminants.

For each contaminant with a cancer slope factor, the EPA calculated a cancer screening value using this equation and constants:

$$\text{Cancer screening level} = \frac{\text{cancer risk level} \times \text{consumer body weight}}{\text{cancer slope factor} \times \text{consumption rate}}$$

where:

Cancer risk level = 10^{-6}
Body weight of adult in general population and of frequent fish consumer = 80 kg
Consumption rate of general population = 32.4 g/d
Consumption rate of frequent fish consumer = 142 g/d

[Note: The 2000 Guidance presented fish meal calculations based on a cancer risk level of 10^{-5}. The EPA is considering updating that factor to 10^{-6} to be consistent with methods for developing water

[2] This consumption rate is based on the recommendation in the U.S. Department of Agriculture and Department of Health and Human Services' *Dietary Guidelines for Americans, 2020-2025* to eat 8-10 ounces per week of seafood.
[3] From EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)* that recommends a default of 142.4 grams/day for subsistence fishers.

quality criteria. To ensure it captured problematic compounds, the EPA used the 10^{-6} cancer risk level in these screening level calculations.]

The EPA analyzed whether the maximum or average concentrations extracted from articles exceeded the cancer screening level for an adult in the general population or for a frequent fish consumer. Some studies reported only averages for a contaminant; some reported only maximums. The EPA considered a contaminant for consideration if the screening level was exceeded by the average tissue concentration, maximum concentration, or both.

Results of Process

EPA developed two draft lists of compounds based on available information:

1. *Contaminants to Monitor for Advisories*: The compounds on this list are found to occur in edible tissue of fish or shellfish at levels of concern to human health and have toxicity information in the form of an EPA oral reference dose, ATSDR minimal risk level, or EPA cancer slope factor. These are new compounds that the EPA is considering adding to its existing list (in 2000 Guidance) of recommended compounds to monitor for fish advisories. The version sent through the peer review process included five PFAS compounds, one cyanotoxin, two flame retardants, and two metals.
2. *Contaminants to Monitor to Watch*: The compounds on this list are those that may need advisories in the future. They are on the list because they have documented concentrations in fish and/or shellfish that could be of concern for human health, based on the generic screening level used in these analyses, but the federal government has not yet developed toxicity values such as reference doses or cancer slope factors for them. The version sent through the peer review process included two cyanotoxins, five flame retardants, seven PFAS compounds, four pharmaceuticals, and three divisions of chlorinated paraffins.

Section 2: Summary of Peer Reviewers' Suggestions

The EPA submitted the process it used to create a list of contaminants to add to the monitoring list in its 2000 Guidance to a group of three of subject matter experts in toxicology and human health risk assessment for an independent, external peer review. The peer reviewers responded to the charge questions and had some suggestions, which the peer review contractor compiled into a report. This section summarizes the reviewer comments by charge question. Appendix 2 contains the complete peer review report.

Charge Question 1: Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?

All three reviewers agreed that the process EPA followed was reasonable, but also indicated that the process would benefit from some revision. One reviewer suggested incorporating toxicity values from databases less focused on North America. Two reviewers noted that using a cancer slope factor as a screening level for lead is highly unusual; both suggested that EPA's Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) model or EPA's Adult Lead Model should be used to develop a screening level. One reviewer recommended that the draft IRIS reference dose values for PFHxS (released after the document that was sent to the peer reviewers was written) and PFNA (not yet released) be used for calculating the screening levels for those compounds.

For calculating a generic screening level for contaminants without established toxicity information, all three reviewers questioned the use of the chronic reference value based upon the PFNA minimal risk level (MRL) produced by ATSDR. One reviewer stated that EPA should use a well-established toxicity value with a high degree of scientific consensus regarding the validity of the value and how it was derived. This reviewer commented this was not the case for PFNA, because IRIS is developing a newer draft assessment for it. Another reviewer stated that the generic screening level based on the ATSDR MRL for PFNA is highly uncertain and that ATSDR MRLs are based on animal data, not human data. The third reviewer expressed that extrapolating the same reference dose across chemical classes seems unnecessary when it is possible to choose the lowest reference dose within each chemical class.

One reviewer suggested updating the screening level equation to better reflect current state practices for implementing fish advisories. This reviewer also noted that, for occurrence data, sample maximums are very unreliable statistics and recommended using a high percentile (e.g., 95^{th} or 99^{th} percentiles) to represent high data values more appropriately. The same reviewer also recommended against using lipid-normalized concentrations and suggested that these values be converted to wet weight concentrations.

Charge Question 2: Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?

All three reviewers agreed that the list of contaminants is reasonable and comprehensive. One reviewer noted that there are other compounds of concern that could be included in the list, but that these contaminants are not well known or well researched; this reviewer indicated that the list is reasonable even without the additional contaminants. Another reviewer noted that some states have already developed fish consumption advisories for many contaminants on the list.

Charge Question 3: Are there additional contaminants that should be included in the "monitor for advisories" list or "monitor to watch" list? If so, what are they, and why should they be included?

Two reviewers suggested including additional contaminants. One reviewer recommended adding 6:2 di- and mono-PAPs and fluorotelomer sulfonates to the lists, as they all have shown high bioconcentration factor (BCF) values in recent studies. Another reviewer suggested adding additional cyanotoxins, such as cylindrospermopsin, anatoxin-a, and saxitoxin to the lists, because harmful algal blooms (HABs) are of current concern. This reviewer noted that cyanotoxin advisories should take into account that HAB exposures are often short-term, not chronic.

Section 3: Changes Made in Response to Peer Reviewer Comments

The EPA has grouped the comments provided by the peer reviewers into areas based on their similarity and described any changes that were made to the process and list of contaminants in response to the peer reviewers' comments.

Area 1: Toxicity Values

Reviewers commented that the EPA should consider expanding the universe of toxicity values used in the screening level calculations beyond those published by U.S. agencies, including EFSA, WHO, and state agencies. They also suggested using an exposure model for lead instead of a cancer slope factor.

In the information considered by the peer reviewers, the EPA had used toxicity information from a list of specific sources, in alignment with the EPA's methodology for developing water quality criteria to protect human health (2010) and corresponding criteria update (2015). That methodology lists eight sources; of those eight the EPA found and used reference doses, cancer slope factors, minimal risk levels, and similar toxicity information from the following sources:

- EPA's Integrated Risk Information System (IRIS) program.
- EPA's Office of Water programs.
- EPA's Office of Land and Emergency Management Provisional Peer Reviewed Toxicity Values (PPRTVs) for the Superfund program.
- U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR).
- California Environmental Protection Agency's Office of Environmental Health Hazard Assessment.

The EPA has elected not to deviate from the process it uses for water quality criteria. In general, states, territories and tribes have the flexibility to monitor for any contaminant, and they can use additional toxicity values than the EPA considered when they calculate and issue fish advisories. The EPA's list of contaminants for monitoring are simply recommendations to the states, Tribes and territories.

To be consistent in its evaluation process, the EPA followed the same process for all contaminants but recognizes that lead is often treated differently. Reviewers suggested using a lead model, but lead exposure models primarily focus on soil contamination as the primary data input, and other exposures like drinking water and fish consumption are used to refine the risk to the receptor from exposures to soil. The relative contribution from specific exposure pathways (e.g., water, diet, soil, ambient air) to blood lead concentrations is situation specific. According to the EPA's *Integrated Science Assessment for Lead* (External Review Draft, 2023, EPA/600/R-23/061), 30 causality determinations were made for human health outcomes from exposure to lead, like cognitive function decrements in children and cardiovascular effects. With each EPA assessment for lead over time (e.g., 2006, 2013), the epidemiologic and toxicological evidence demonstrated that progressively lower blood lead levels or lead exposures are associated with cognitive deficits in children. The EPA decided to keep lead on the monitoring list for fish advisories because there is no known safe level of exposure to lead.

Area 2: Generic screening level

Regarding the EPA's calculation of a generic screening level for contaminants without established toxicity information, all three reviewers questioned the use of the chronic reference value based upon the minimal risk level for PFNA produced by the ATSDR. One reviewer stated that the EPA should use a well-established toxicity value with a high degree of scientific consensus regarding the validity of the

value and how it was derived. This reviewer commented this was not the case for PFNA, because IRIS is developing a draft assessment for it. Another reviewer stated that the generic screening level based on the ATSDR MRL for PFNA is highly uncertain and that ATSDR MRLs are based on animal data, not human data. The third reviewer expressed that extrapolating the same reference dose across chemical classes seems unnecessary when it is possible to choose the lowest reference dose within each chemical class.

The EPA investigated using the lowest reference dose within each class of contaminants. Every contaminant class that contained a substance needing a generic screening level had at least one compound with a reference dose from the water quality criteria's list of sources except paraffins and pharmaceuticals. The EPA used oral human exposure doses for paraffins, and screening doses for pharmaceuticals in place of reference doses. The EPA used the lowest toxicity value (i.e., reference dose, human exposure dose, or screening dose) in each contaminant class and calculated screening levels for each class of contaminants, as described in each of the following subsections.

Cyanotoxins

For cyanotoxins, the EPA used the lowest available reference dose, which was 0.05 µg/kg-d for microcystins from the EPA's *Health Effects Support Document for the Cyanobacterial Toxin Microcystins* (2015). Concentrations of BMAA (β-methylamino-L-alanine) and DABA (2,4-diaminobutyric acid dihydrochloride) in fish were higher than the screening level calculated using the microcystins reference dose, so the EPA retained them on the final list of contaminants.

Flame retardants

For flame retardants, the EPA used the lowest available reference dose for oral exposure, which was 1 x 10^{-4} mg/kg-d for both BDE-47 and BDE-99 from the EPA's Integrated Risk Information System. Concentrations in fish of all the flame retardants without toxicity information were lower than the screening level calculated using the reference dose for BDE-47 and BDE-99, so the EPA removed BDE-49, BDE-100, Dechlorane 602, Dechlorane 604, and decabromodiphenyl ethane (DBDPE) from the final list of contaminants.

PFAS

The PFAS group was handled slightly differently. Based on input from the EPA's Office of Research and Development and as published in the *Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)* (External Review Draft, 2023), the PFAS compounds were separated into four groups based on whether they were long- or short-chain carboxylic or sulfonic acids, as shown in Table 1. PFOSA was grouped with the long-chain sulfonic acids.

Table 1: Characterization System of Short-Chain and Long-Chain Perfluoroalkyl Acids[a]

Total number of carbons	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number of fluorinated carbons	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Perfluorocarboxylic acids (PFCAs)	**Short-chain PFCAs**					**Long-chain PFCAs**		
	PFPrA	PFBA	PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA
Number of fluorinated carbons	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Perfluorosulfonic acids (PFSAs)	PFPS	PFBS	PFPeS	PFHxS	PFHpS	PFOS	PFNS	PFDS
	Short-chain PFSAs			**Long-chain PFSAs**				

Notes: PFPrA = perfluoropropanoic acid; PFBA = perfluorobutanoic acid; PFPeA = perfluoropentanoic acid; PFHxA = perfluorohexanoic acid; PFHpA = perfluoroheptanoic acid; PFOA = perfluorooctanoic acid; PFNA = perfluorononanoic acid; PFDA = perfluorodecanoic acid; PFPS = perfluoropropanesulfonic acid; PFBS =

perfluorobutanesulfonic acid; PFPeS = perfluoropentanesulfonic acid; PFHxS = perfluorohexanesulfonic acid; PFHpS = perfluoroheptanesulfonic acid; PFOS = perfluorooctanesulfonic acid; PFNS = perfluorononanesulfonic acid; PFDS = perfluorodecanesulfonate. For brevity, Table 1 only includes perfluoroalkyl acids of 3-10 carbons; the long-chain class of PFCAs and PFSAs can be expanded considerably.

[a] Table 1-3 from EPA's *Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)* (2024); modification of Table 2-2 from ITRC's *Per- and Polyfluoroalkyl Substances Technical and Regulatory Guidance* (2022).

The EPA considered the lowest available draft and final toxicity data within each PFAS group, as shown in Table 2, to calculate the group's generic screening level for those PFAS without a reference dose (RfD) or minimal risk level.

Table 2: Toxicity Information Used for PFAS Groups

PFAS Group Name	PFAS in Group Found in Fish and/or Shellfish	Compound with Lowest Human Health Toxicity Value and its Value (Source)
Short-chain PFCAs	PFBA, PFHxA, PFHpA, PFPeA	PFHxA: 5×10^{-4} mg/kg-d (final RfD - IRIS)
Long-chain PFCAs	PFDA, PFDoA, PFNA, PFOA, PFTeDa, PFTrDA, PFUndA	PFDA: 4×10^{-10} mg/kg-d (draft RfD -IRIS) PFOA: 3×10^{-8} mg/kg-d (final RfD - OW)
Short-chain PFSAs	PFBS	PFBS: 3×10^{-4} mg/kg-d (final human health toxicity value - PPRTV)
Long-chain PFSAs	PFDS, PFHpS, PFHxS, PFOS, PFOSA	PFHxS: 4×10^{-10} mg/kg-d (draft RfD - IRIS) PFOS: 1×10^{-7} mg/kg-d (final RfD - OW)

Using the reference dose for PFHxA for the short-chain PFCAs without a toxicity value resulted in a screening level higher than the concentrations of PFHpA and PFPeA that were found in fish, so the EPA did not add them to the final list of recommended contaminants to monitor. PFBA and PFHxA had screening levels based on published toxicity values; these were also higher than the fish tissue concentrations, so the EPA did not add PFBA and PFHxA to the final list.

Using either the draft reference dose for PFDA or the final reference dose for PFOA for the long-chain PFCAs without a toxicity value resulted in a screening level lower than the concentrations of PFDoA, PFTeDA, PFTrDA and PFUnDA that were found in fish and shellfish, so they remained on the final list of recommended contaminants to monitor. PFDA, PFNA, and PFOA had screening levels based on published toxicity values; these were also lower than the fish tissue concentrations, so PFDA, PFNA, and PFOA remained on the final list.

For short-chain PFSAs, the only one that was found in fish was PFBS, which has a reference dose. PFBS concentrations in fish did not exceed the calculated screening levels, therefore the EPA did not include it on the final list.

Using either the draft reference dose for PFHxS or the final reference dose for PFOS for the long-chain PFSAs without a toxicity value resulted in a screening level lower than the concentrations of PFDS, PFHpS and PFOSA that were found in fish, so PFDS and PFOSA remained on the final list and PFHpS was added to the list. PFHxS and PFOS had screening levels based on published toxicity values; these were also lower than the fish tissue concentrations, so they remained on the final list.

Paraffins

The contaminant class of paraffins did not have a compound with a reference dose that could be used to calculate a generic screening level. The EPA's Office of Pollution Prevention and Toxics developed oral human exposure doses for paraffins in its *TSCA New Chemicals Review Program Standard Review Risk Assessment on Medium-Chain Chlorinated Paraffins (PMN P-12-0282, P-12-0283) and Long-Chain Chlorinated Paraffins (PMN P-12-0284)* (2015). The EPA used those human exposure doses in place of a reference dose in the screening level equations and determined that paraffins concentrations found in fish were not high enough to exceed the screening levels.

Pharmaceuticals

The other contaminant class without a reference dose at the time of the peer review was pharmaceuticals. After the peer review, for pharmaceuticals the EPA switched from using a generic screening level to using information from the draft *Human Health Drinking Water Benchmarks for Pharmaceuticals* produced by the Office of Water (one of the allowable sources in the process). A screening level for the general population for each pharmaceutical found in fish were calculated using the screening doses in the draft benchmarks document. Screening doses were calculated by dividing the lowest therapeutic doses from FDA labels by a composite uncertainty factor of 3,000 to account for interspecies extrapolation, intraspecies variation, subchronic-to-chronic study extrapolation, extrapolation from a lowest-observed-adverse effect level (LOAEL) (i.e., lowest therapeutic dose) to a no-observed-adverse effect level (NOAEL), and database deficiencies. The screening dose was treated as equivalent to a reference dose in the screening level equations. Norfluoxetine, norverapamil, sulfadimethoxine, and triclocarban did not have screening doses in the pharmaceutical benchmarks document. For those four compounds, the EPA used the lowest screening dose for compounds in the pharmaceutical category that were found in fish, which was 8.3×10^{-6} mg/kg-d for amphetamine, to calculate a generic screening level. The concentrations of those four compounds in fish were lower than the screening level, so the EPA did not add them to the contaminant list.

Concentrations in fish no longer exceeded the screening levels for these pharmaceuticals:

- Metformin.
- Sertraline.
- Sulfadimethoxine.

The EPA removed those pharmaceuticals from the draft list of contaminants to monitor. Only amphetamine had concentrations in fish that exceeded the screening levels, so it remained on the list.

Summary of actions resulting from change in process to generic screening level

Using the generic screening levels calculated for each contaminant class and PFAS group and using the human exposure doses for paraffins and screening doses for pharmaceuticals yielded the following changes from the draft list to the final list.

Concentrations in fish fillets and whole fish that previously had exceeded the initial generic screening level based on ATSDR's MRL for PFNA did not exceed the newly calculated screening levels for these contaminants (five flame retardants, three classes of paraffins, and three pharmaceuticals):

- BDE-49.
- BDE-100.
- Dechlorane 602.
- Dechlorane 604.

- Decabromodiphenyl ethane (DBDPE).
- Short-chain chlorinated paraffins.
- Medium-chain chlorinated paraffins.
- Long-chain chlorinated paraffins.
- Metformin.
- Sertraline.
- Sulfadimethoxine.

Concentrations in fish fillets and whole fish that previously did not exceed the initial generic screening level exceeded the newly calculated screening levels for this contaminant (one PFAS):

- PFHpS.

As a result of the changes to the generic screening levels, the EPA removed the five flame retardants, three paraffin classes, and three pharmaceuticals from the draft list. In addition, the EPA added the one PFAS compound to the list of contaminants to watch.

Area 3: Contaminant concentration data

For each contaminant, the EPA compared the screening levels to the average and maximum concentrations in fish and shellfish that were extracted from the journal articles reviewed. One reviewer raised concerns with the use of maximum and lipid-weight concentrations.

Maximum concentrations

The reviewer said a sample maximum is an unstable summary statistic and subject to extreme results but recognized that the EPA was limited by what is reported in the literature.

Post peer review, the EPA calculated 75th percentiles of concentration data maximums for contaminants on the draft list and compared those to the screening levels. As a result, BDE-99 no longer exceeded any screening levels and was removed from the draft list. In addition, there was not enough data to calculate a 75th percentile concentration for PFProPrA and thallium, so they were removed from the draft list.

Lipid weight concentrations

The EPA did not include lipid weight concentration data in its analyses unless the only data for a contaminant was reported in lipid weight form. This circumstance was true for only three compounds that were placed on the draft list of contaminants to monitor – the flame retardants Dechlorane 602, Dechlorane 604, and Decabromodiphenyl ethane (DBDPE).

The EPA converted the lipid weight concentrations for these three compounds to wet weight concentrations using total fat content percentages from Table 10-125 (e.g., 6.61% for "trout, mixed species") and Equation 10-7 in the *Environmental Factors Handbook* (2011):

> "… wet-weight residue levels in fish may be estimated by multiplying the levels based on fat by the fraction of fat per product as follows:
>
> $$C_{ww} = C_{lw} \left[\frac{L}{100}\right]$$
>
> where:
>
> C_{ww} = wet-weight concentration, C_{lw} = lipid-weight concentration, and L = percent lipid (fat) content."

When the EPA calculated revised screening levels for each contaminant class and used the converted wet weight concentrations, the three flame retardants no longer had concentrations that exceeded the screening levels and the EPA removed them from the draft list.

Area 4: Additional contaminants

One reviewer recommended adding fluorotelomer sulfonates to the contaminant list. The study the reviewer referenced was performed in Norway and was on primarily non-U.S. species and/or measured contaminant levels in parts that the EPA's fish advisory program recommends not eating (e.g., crab hepatopancreas, fish liver) so it did not meet our search parameters, but the EPA will continue to be on the lookout for contaminants in fish that should be added to the monitoring list.

Another reviewer suggested adding additional cyanotoxins, such as cylindrospermopsin, anatoxin-a, and saxitoxin to the lists**.** In its analyses performed before the peer review, the EPA analyzed the data it had found for those toxins, but concentrations were not high enough to exceed the screening levels. If there is an active harmful algal bloom, advisory programs could monitor and analyze fish and shellfish for the relevant cyanotoxin and issue a short-term consumption advisory, if warranted.

General comments

Comments on specific wording changes for the process will be addressed when the EPA updates the applicable section of the *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories*. The comment on updating the screening level equation to include a hazard quotient and relative source contribution (RSC) to account for additional exposure pathways will be addressed when the EPA shares its suite of fish advisory equations with a set of peer reviewers, as part of the update to the fish advisory guidance. The draft reference dose for PFHxS that was released by IRIS after the development of the document that went to the peer reviewers was incorporated into the calculations; PFHxS remains on the list of contaminants to monitor.

Revisions to the Contaminant List After the Peer Review

Table 3 summarizes the changes that the EPA made to the draft list of contaminants after reviewing the peer reviewers' comments and making changes to the process.

Table 3: Changes to Contaminant Status

Contaminant class	Retained	Added	Dropped
Chlorinated paraffins			Short-, medium-, and long-chain
Cyanotoxins	BMAA DABA Microcystins		
Flame retardants	BDE-47		BDE-49 BDE-99 BDE-100 Dechlorane 602 Dechlorane 604 DBDPE
Metals	Lead		Thallium
PFAS	PFDA PFDS	PFHpS	PFPrOPrA

Contaminant class	Retained	Added	Dropped
	PFDoA PFHxS PFNA PFOA PFOS PFOSA PFTeDA PFTrDA PFUnDA		
Pharmaceuticals	Amphetamine		Metformin Sertraline Sulfadimethoxine

Section 4: Final Additions to Contaminants to Monitor

The EPA has finalized which new contaminants that it will recommend fish and shellfish advisory programs include in their monitoring programs. These contaminants have been found to occur in the edible tissue of fish and shellfish at concentrations that may be of concern for human health. The EPA has separated the lists into two groups based on the availability of toxicity information.

1. The first list, "Contaminants to monitor for advisories" (shown in Table 1), contains new contaminants for which the EPA or other federal agencies have released measures of oral toxicity in humans (e.g., reference dose, cancer slope factor). The EPA recommends that advisory programs use this list for monitoring and issuing advisories with consumption limits.
2. The second list, "Contaminants to monitor to watch" (shown in Table 2), contains contaminants for which the EPA or other federal agencies have not yet released assessments of the effects on human health. The EPA recommends that advisory programs monitor for compounds on this list to determine if they are accumulating in fish in local waters. The advisory programs could calculate their own or use another agency's scientifically based measures of oral toxicity in humans to calculate consumption limits, or wait for such values to be released from a federal agency.

Table 1. New contaminants to monitor for fish and shellfish advisories

Contaminant Group	Contaminant
Cyanotoxins	Microcystins
Flame retardants	BDE-47
Metals	Lead
Pharmaceuticals	Amphetamine
PFAS	Perfluorodecanoic acid (PFDA) Perfluorohexane sulfonic acid (PFHxS) Perfluorononanoic acid (PFNA) Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS)

Table 2. Contaminants to monitor to watch

Contaminant Group	Contaminant
Cyanotoxins	BMAA (β-methylamino-L-alanine) DABA (2,4-diaminobutyric acid dihydrochloride)
PFAS	Perfluorodecanesulfonic acid (PFDS) Perfluorododecanoic acid (PFDoA) Perfluoroheptanesulfonic acid (PFHpS) Perfluorooctanesulfonamide (PFOSA) Perfluorotetradecanoic acid (PFTeDA) Perfluorotridecanoic acid (PFTrDA) Perfluoroundecanoic acid (PFUdA, PFUnA, PFUnDA)

Appendix 1: Process For Selecting Contaminants To Monitor In Fish Advisory Programs That Was Sent to Peer Reviewers

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Overview

State, tribal, and territorial fish and shellfish advisory programs should monitor and analyze fish and shellfish in waterbodies within their jurisdictions for contaminants. When contaminants occur in high enough concentrations to potentially affect the health of people eating fish and shellfish from those waters, EPA recommends that those programs issue advisories regarding consumption to protect the consumers. To help state, tribal, and territorial fish and shellfish advisory programs, EPA recommends a set of contaminants to monitor in its 2000 version of Volume 1 of *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* (2000 Guidance), shown in Appendix Table A-1. In updating this guidance, EPA reviewed scientific literature and determined that additional contaminants should be monitored. The process and new contaminants identified as a result of that process are described here.

EPA performed a literature search to identify scientific information on the contaminants that bioaccumulate in fish and shellfish and their corresponding concentrations. After searching multiple databases, using a specified set of search terms, EPA extracted references, removed duplicates, and screened articles to remove any that contained fish not found in U.S. waters or contained concentration data only from lab studies. After extracting maximum and average concentrations of contaminants from the papers, EPA used these concentrations in fish advisory equations to determine if the levels found would exceed thresholds for restrictions in consumption of fish.

This document describes the steps for screening scientific literature for compounds that bioaccumulate in aquatic animals and deciding on their potential inclusion on the lists of analytes that fish advisory programs should monitor.

Background

States, territories, and tribes issue consumption advisories for substances that occur in fish and shellfish at levels of concern to human health. Consumption advisories issued by states and tribes include freshwater, estuarine, and coastal marine fish and shellfish species. The selection of appropriate target analytes in fish and shellfish contaminant monitoring programs is essential to the issuance of these advisories. For identifying potential analytes, the primary necessary element is evidence that the substance occurs in the edible tissue of consumed fish species at a concentration that may cause exposure to be of concern for human health for identified health endpoints.

Contaminant occurrence in fish tissue generally requires three conditions:

1. The compound must have been released to the environment in sufficient quantity.
2. The compound must be persistent in water and/or air for transport in the environment once released.
3. The chemical nature of the substance must cause it to bioaccumulate in food webs due to an affinity for fish tissues, which vary both by chemical and fish species characteristics.

Contaminants in fish must be persistent and bioaccumulative in nature to advance through the food web and be ingested by humans to an extent that it could impact the health of consumers. Persistent substances will avoid being dissolved in the aquatic environment and will remain

relatively intact while being transported in water and/or atmospherically. Persistence is required because in the aquatic environment, chemical compounds are subject to the considerable solvent power of the polar water molecule and other chemical and physical factors. These include effects of the impingement of light (UV) and dissolved gasses in the water column, and interaction with other dissolved constituents in water, especially in marine environments.

Bioaccumulation is a key mechanism required for compounds to occur at concentrations in fish that can affect human health, and therefore is needed for a compound to be a candidate for an advisory. In finfish, the mechanism for bioaccumulation is predation and resulting bio-magnification up through the food chain. Starting with micro-organisms in sediment or the water column, predation by larger species causes persistent compounds with an affinity for various tissue types (e.g., lipids, muscle, bloody organs, blood) to increase at successive trophic levels to ultimate concentrations in the fish (top predators usually contain the highest concentrations). Because shellfish filter feed, they can take up toxic substances directly from the water column, which they then store and accumulate. The accumulated compounds can become harmful to consumers when ingested.

Developing an advisory for a compound generally requires data on its toxic effects on humans. Reproductive, developmental (including neurodevelopmental), hepatotoxic (liver), and immunotoxic are among the most common types of human health effects from exposure to contaminants in fish. These effects can be quantified by a measure of oral toxicity. Two measures used in assessing toxicity and risk to humans through a fish consumption pathway are reference dose and cancer slope factor:

- *Reference dose (RfD)*: a metric used to denote an amount of a contaminant that can be consumed over a time period without adverse health effects. RfDs are typically expressed as the ingestion in milligrams (mg) of a contaminant per kilogram (kg) of body weight (of the consumer) per day. It specifically indicates an amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime), with a measure of uncertainty, without suffering a deleterious effect.
- *Cancer slope factor (CSF)*: a metric used to describe the increase in cancer risk resulting from a given rate of exposure to a substance, usually over a lifetime. Cancer slope factors are typically expressed as typically expressed in units of proportion of a population affected per milligram of substance per kilograms of body weight per day (expressed in units of reciprocal dose $(mg/kg\text{-}day)^{-1}$).

Literature Search

EPA initiated a systematic screening process (not a full-blown systematic review) to identify any additional relevant compounds that are not currently included in the 2000 Guidance. EPA developed a literature review protocol to compile peer-reviewed articles that provide a basis for choosing any new analytes. Several environmental science, health, and toxicology databases were searched for relevant peer-reviewed publications using keywords and inclusion and exclusion criteria. These combined efforts resulted in more than 600 articles being compiled for further review.

Pre-search Definition of Screening Criteria

Before beginning the literature search, EPA identified criteria in five key areas for selecting publications:

1. Publication status
2. Publication date
3. Publication language
4. Fish species discussed
5. Compounds analyzed in the study.

EPA also defined screening factors for potential contaminants. EPA determined that each compound should preferably meet all these criteria:

1. Present in fish and/or shellfish
2. Potential to bioaccumulate
3. Prevalent and persistent in the environment
4. Associated with evidence that eating fish and shellfish is a potential exposure pathway
5. Presence of toxicity information, preferably a reference dose or cancer slope factor generated by the federal government (e.g., EPA, ATSDR)
6. Quantifiable in fish tissue with a validated analytical method capable of determining its concentration at levels of human health relevance.

Article Inclusion Criteria

EPA included only articles that were:

- Peer-reviewed
- Published in 2000 or later (to capture information published after the 2000 Guidance)
- Written in English.

Sources Searched

EPA searched environmental science, health, and toxicology databases for relevant articles:

- PubMed
- PubChem
- Web of Science
    - includes Science Citation Index Expanded, Social Sciences Citation Index, and Conference Proceedings, Citation Indexes for Science and for Social Science and Humanities
- Environmental Science and Pollution Management
    - includes Aquatic Science and Fisheries Abstracts, Aquatic Pollution and Environmental Quality, Water Resources Abstracts, TOXLINE, Toxicology Abstracts, Environmental Abstracts, Pollution Abstracts, and Conference Papers Index
- Science Direct
- Toxline

EPA also utilized an internal literature search that had been conducted for harmful algal blooms (HABs) and HAB toxins.

Keywords

The keywords used to search the literature are listed by category in the following bullets.

- Target analytes
    - PCBs or contaminant or constituent or contamination or emerging contaminant or aquatic contaminant or chemicals or pollutants or metals or pesticides
- Aquatic animal types
    - Finfish or fish or freshwater turtles or shellfish or bivalves or crustaceans or mollusks
    - AND edible tissue or muscle tissue
- Chemistry
    - Persistent, halogenated, chlorinated, brominated, perfluorinated, cyclic, polycyclic, ortho, meta, para
- Bioaccumulation
    - Accumulation or bioconcentration or bioaccumulation or BCF or BAF or bioaccumulate or bioconcentrate or bioaccumulative
- Toxicity
    - Toxic or toxicity or human health benchmark or oral toxicity or RfD or reference dose or cancer or slope factor
- Location
    - United States, Alaska, Hawaii; freshwater, estuarine and marine waters

In addition to searches using the keywords above that were selected to cast a wide net, EPA consulted publications by federal agencies (e.g., EPA, NIEHS in NIH), states (WA, MN, MI, ME, NY), the Great Lakes Alliance, and articles listing potential persistent organic pollutants (e.g., Brown and Wania, 2008; Sun et al, 2016; Muir et al, 2006; Stockholm Convention List) to identify candidate compounds previously identified by other researchers. Then EPA conducted literature searches pairing each compound name or its CAS number with these keywords:

- Fish, fish tissue, or concentration

Weight of evidence analysis

EPA screened the articles collected during the literature search, extracted information from the peer-reviewed publications, and applied weight of evidence (WOE) points. Each publication received one point based on whether it included information on the contaminant's detection in fish, BCF or BAF data, oral toxicity data, and species found in the U.S. For example, if an article had analyte concentration data in a U.S. fish species but no toxicity data nor BCF/BAFs, it received two points. The points assigned ranged from a minimum of zero to a maximum of four.

Initially only articles with a WOE total of 3 or 4 points were included for further analysis. However, EPA determined that requiring papers to have concentration data in fish tissue, BCF/BAF data, and toxicity data artificially restricted the number of potential contaminants. Articles with a WOE total of 2 or higher were examined for relevance and data.

Preliminary Contaminant List Compilation, Data Extraction, and Exclusions

EPA developed a preliminary list of 242 potential contaminants mentioned in the articles, compiled during the literature search, with a WOE total of 2 or more (Appendix Table A-2).

Contaminants were found in the following classes:

- Antibacterial, antibiotic, and antimicrobial compounds
- Brominated compounds
- Chlorinated compounds
- Cyanotoxins and neurotoxins
- Flame retardants
- Hormones
- Industrial byproducts
- Inorganics
- Metabolites
- Metals
- Organophosphorus esters
- Nanoparticles
- PCBs
- Personal care products
- Pesticides
- PFAS compounds
- Pharmaceuticals
- Phthalates
- Polychlorinated naphthalenes
- Polycyclic aromatic hydrocarbons
- Sulfonamides
- Other

EPA then extracted concentration data from the articles. The articles EPA reviewed for the compounds' concentration data mining effort contained concentration data in different units, value formats (e.g., averages, ranges or maxes), and fish tissue types. After extracting the data from the articles, EPA sorted the data by units. If articles did not provide enough information to determine concentration units, EPA removed them from the dataset.

Articles reported concentrations in three different units: wet weight, lipid weight, and dry weight. EPA prioritized wet weight data because it is the most common unit used for benchmark analyses. To use the concentration data presented as lipid or dry weight, EPA needed additional % lipid or % moisture data, which was often not available in the articles reviewed. Therefore, if EPA compiled data for a compound in more than one unit (e.g., there was lipid and wet weight data), EPA used only the wet weight data in the calculations. Some compounds did not have any concentrations in wet weight units; these were kept as lipid or dry weight and not modified.

The articles EPA reviewed for compounds contained concentration data not only for fillet tissue, but also for whole body, organs, blood, etc. Each article EPA reviewed had a different study objective, and, thus, different fish and shellfish tissues were analyzed. Tissue data were sorted into several categories: fillet, whole body, organs (including liver, kidney, blood and eggs), shellfish only, and eel only. Articles which did not specify fish tissue were removed from the literature review.

There were data from more than 75 species in the concentration data mining effort. Data from non-native species were removed unless they have been found in a U.S waterbody in the last 10 years. Only two non-native species were retained in this list: Brown trout and Common carp. These species are invasive and abundant in U.S. waters.

Fish advisory programs managers are most interested in what potentially affects fish in ambient waters. If the studies were not analyzing ambient conditions (e.g., fish were dosed in a lab study), then those concentrations were removed.

After sorting the data by tissue type and species, EPA collected maximum and average concentration data, and converted data, where necessary, to ng/g. Not all articles provided maximum and average values. If a range of concentrations was reported, where possible, the maximum value from the concentration range was used as the maximum value. Maximum values

reported as an inequality (e.g., >6) were excluded. Average concentrations reported as a range or with an inequality symbol (e.g., <4.8) were excluded.

EPA removed compounds without concentration data, compounds already on the monitoring list in the 2000 Guidance, and mixtures (e.g., BDE-119 + BDE-120, sum of PFAS), and this resulted in lists of 49 potential contaminants with fillet data, 55 with whole fish data, and 14 with shellfish data (Appendix Tables A-3, A-4, and A-5).

Researched Toxicity Values

After extracting toxicity information from articles and U.S. government sources such as EPA IRIS and ATSDR, EPA searched for additional and updated toxicology data.

EPA searched the following eight peer-reviewed, publicly available sources, as described in its 2015 update of human health ambient water quality criteria, to obtain the toxicity values (reference dose, minimum risk level, and/or cancer slope factor) and used them in screening level calculations, in this order of preference:

1. EPA's Integrated Risk Information System (IRIS) program
2. EPA's Office of Pesticide Programs Pesticide Chemical Search
3. EPA's Office of Pollution Prevention and Toxics Existing Chemicals
4. EPA's Office of Water Water Topics
5. EPA's Office of Solid Waste and Emergency Response Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV)
6. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) Toxic Substances Portal
7. Health Canada
8. California Environmental Protection Agency's Office of Environmental Health Hazard Assessment - All Public Health Goals

For PFAS compounds, EPA used the reference doses for PFOS, PFOA, PFNA, PFBS, and PFHxS that were used in the proposed national primary drinking water regulation released on March 14, 2023, and the reference doses in IRIS for PFBA, PFBS, PFDA, and PFHxA. EPA did not use toxicity values from any sources other than those listed in this section, because of the variability of methods applied and inconsistency of the existence of adequate quality control documentation.

Screening Level Calculations and Analyses

For each contaminant with a non-cancer toxicity value, EPA calculated a non-cancer screening value using this equation from the 2000 Guidance:

$$\text{Non-cancer screening level} = \frac{\text{reference dose} \times \text{consumer body weight}}{\text{consumption rate}}$$

where:

Body weight of adult in general population and of frequent fish consumer = 80 kg
Body weight of pregnant person = 75 kg

Consumption rate of adult in general population and pregnant person = 8 oz/week * 28.35 g/oz * 1 week/7d = 32.4 g/d[1]
Consumption rate of frequent fish consumer = 142 g/d[2]

The reference doses were provided in mg/kg-day. EPA multiplied them by 1000 to convert them into micrograms/kg-day in order to calculate non-cancer screening levels in micrograms per gram (ppm). Concentration data were all converted to micrograms per gram, and the non-cancer screening levels were compared to the concentration data found in the scientific literature.

EPA analyzed whether:

- The maximum concentration, which is the highest concentration found in reported maximum concentrations extracted from articles, exceeds the non-cancer screening level for an adult in the general population
- The maximum concentration exceeds the non-cancer screening level for a pregnant person
- The maximum concentration exceeds the non-cancer screening level for a frequent fish consumer
- The average concentration, which is the average of the reported average concentrations extracted from articles, exceeds the non-cancer screening level for an adult in the general population
- The average concentration exceeds the non-cancer screening level for a pregnant person
- The average concentration exceeds the non-cancer screening level for a frequent fish consumer

EPA also calculated whether the maximum concentration and average concentration were within 75 percent of the non-cancer screening level for an adult in the general population to see if there were compounds that could be problematic but not currently accumulating to problematic levels. EPA did not find additional compounds to include as a result of those analyses.

A contaminant's presence in fish does not necessarily indicate a human health risk exists. For the contaminants *without* non-cancer toxicity values, EPA calculated a "generic" screening level to capture contaminants with fish tissue concentrations high enough to potentially be a human health concern after reference doses are developed. In its screening level calculation, EPA used the lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed) available among the contaminants found in fish. The lowest reference dose for compounds that were considered for inclusion on the monitoring list in this evaluation is 3×10^{-6} mg/kg-d (PFNA), which was then multiplied by 1000 to convert to micrograms/kg-day. The calculated "generic" screening level was 7.41×10^{-3} µg/g. Concentration data found in the

[1] This consumption rate is based on the recommendation in the U.S. Department of Agriculture and Department of Health and Human Services' *Dietary Recommendations for Americans, 2020-2025* to eat 8-10 ounces per week of seafood.
[2] From EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (2000) that recommends a default of 142.4 grams/day for subsistence fishers.

scientific literature were all converted to micrograms per gram, and the screening levels were compared to the concentration data. EPA analyzed whether:

- The maximum concentration exceeds the "generic" non-cancer screening level
- The average concentration exceeds the "generic" non-cancer screening level

For each contaminant with a cancer slope factor, EPA calculated a cancer screening value using this equation and constants:

$$\text{Cancer screening level} = \frac{\text{cancer risk level} \times \text{consumer body weight}}{\text{cancer slope factor} \times \text{consumption rate}}$$

where:

Cancer risk level = 10^{-6}
Body weight of adult in general population and of frequent fish consumer = 80 kg
Consumption rate of general population = 32.4 g/d
Consumption rate of frequent fish consumer = 142 g/d

[Note: EPA's 2000 Guidance presented fish meal calculations based on a cancer risk level of 10^{-5}. EPA is considering updating that factor to 10^{-6} to be consistent with methods for developing water quality criteria. To be conservative and ensure it captured problematic compounds, EPA used the 10^{-6} cancer risk level in these screening level calculations.]

To calculate cancer screening levels in micrograms per gram (ppm), EPA multiplied the cancer slope factors by 1000, converting them from mg/kg-day into micrograms/kg-day. After converting concentration data to micrograms per gram, EPA compared the cancer screening levels to the concentration data.

EPA analyzed whether the:

- Maximum concentration exceeds the cancer screening level for an adult in the general population
- Maximum concentration exceeds the cancer screening level for a frequent fish consumer
- Average concentration exceeds the cancer screening level for an adult in the general population
- Average concentration exceeds the cancer screening level for a frequent fish consumer

Results of Comparing Concentration Data to Screening Levels

The following subsections describe which contaminants exceeded the specific and generic non-cancer and cancer screening levels in fillet and whole fish data.

Contaminants exceeding screening levels in fillet data

The 10 analytes in Table 1 had concentrations in fillet tissue that exceeded one or more of the screening levels that were calculated for each compound. The table shows which screening levels were exceeded (cancer and/or non-cancer for adult in general population, pregnant person, and/or

frequent fish consumer) and which data type (average concentration, maximum concentration, or both) exceeded the screening level.

Table 1. Contaminants exceeding screening levels in fillet data

Contaminant	Reason on list
BDE-47	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person & frequent fish consumer
BDE-99	Maximum concentration exceeds non-cancer screening level for frequent fish consumer
Lead	Maximum concentration exceeds cancer screening levels for adult in general population and frequent fish consumer
Microcystins	Maximum concentration and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFDA	Maximum concentration and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFHxS	Maximum concentration exceeds non-cancer screening level for frequent fish consumer
PFNA	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFOS	Maximum and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer and cancer screening levels for adult in general population and frequent fish consumer
PFOA	Maximum concentration and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
Thallium	Maximum concentration and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer

(Note: BDE-47, BDE-99, lead, PFHxS, and PFNA did not have any average concentration data to extract from literature.)

Contaminants exceeding screening levels in whole fish data

The eight analytes in Table 2 had concentrations in whole fish tissue that exceeded one or more of the screening levels that were calculated for each compound. The table shows which screening levels were exceeded (cancer and/or non-cancer for adult in general population, pregnant person, and/or frequent fish consumer) and which data type (average concentration, maximum concentration, or both) had a value that exceeded the screening level.

Table 2. Contaminants exceeding screening levels in whole fish data

Contaminant	Reason on list
BDE-47	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
BDE-99	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
Lead	Maximum concentration exceeds cancer screening levels for adult in general population and frequent fish consumer
PFDA	Maximum and average concentration exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFHxS	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFNA	Maximum concentration exceeds non-cancer screening level for frequent fish consumer
PFOA	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person and frequent fish consumer
PFOS	Maximum and average concentration exceed non-cancer screening levels for adult in general population, pregnant person and frequent fish consumer

(Note: lead and PFOA did not have average concentration data to extract from literature.)

Contaminants exceeding screening levels in shellfish data

The five analytes in Table 3 had concentrations in shellfish that exceeded one or more of the screening levels calculated for each compound. The table shows which screening levels were exceeded (cancer and/or non-cancer for adult in general population, pregnant person, and/or frequent fish consumer) and which data type (average concentration, maximum concentration, or both) had a value that exceeded the screening level.

Table 3. Contaminants exceeding screening levels in shellfish data

Contaminant	Reason on list
Microcystins	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer and average concentration exceeds non-cancer screening level for frequent fish consumer
PFDA	Maximum and average concentrations exceed non-cancer screening levels for adult in general population, pregnant person, and frequent fish consumer
PFNA	Maximum concentration exceeds non-cancer screening levels for adult in general population, pregnant person and frequent fish consumer and average concentration exceeds non-cancer screening level for frequent fish consumer
PFOA	Maximum and average concentrations exceed non-cancer screening levels for adult in general population, pregnant person and frequent fish consumer
PFOS	Maximum and average concentrations exceed non-cancer and cancer screening levels for adult in general population, pregnant person and frequent fish consumer

Contaminants exceeding "generic" screening level in fillet data

For contaminants without an EPA RfD, EPA calculated a generic screening level using the most stringent RfD of the compounds found in fish tissue: 3×10^{-6} mg/kg-d. This resulted in a screening level of 0.00741 µg/g. The 12 analytes in Table 4 had concentrations in fillet tissue that exceeded the generic screening level. The table also shows which data type (average concentration, maximum concentration, or both) had a value that exceeded the screening level.

The analytes in Table 4 all had maximum concentrations in fillet tissue that exceeded the generic screening level, except the HAB toxin DABA, for which there was only average concentration data and that exceeded the screening level. In addition to the exceedances of screening levels for maximum concentrations, BMAA also had average concentration data that exceeded the screening level. The average concentration data for PFDoA, PFOSA, and PFUnA did not exceed the screening level; the rest did not have average concentration data.

Table 4. Contaminants exceeding generic screening level in fillet data

Analyte	Concentration type that exceeds the generic screening level
BMAA (β-methylamino-L-alanine)	Maximum concentration Average concentration
DABA (2,4-diaminobutyric acid dihydrochloride)	Average concentration[2]
Dechlorane 602[3]	Maximum concentration[1]
Medium chain chlorinated paraffins	Maximum concentration[1]
Perfluorodecanesulfonic acid (PFDS)	Maximum concentration[1]
Perfluorododecanoate (PFDoA)	Maximum concentration
Perfluorooctanesulfonamide (PFOSA)	Maximum concentration
Perfluorotetradecanoic acid (PFTeDA)	Maximum concentration[1]
Perfluorotridecanoate (PFTrDA)	Maximum concentration[1]
Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)	Maximum concentration
Perfluoro-2-propoxypropanoic acid (PFPrOPrA)	Maximum concentration[1]
Short chain chlorinated paraffins	Maximum concentration[1]

[1] No average data was extracted for this compound.

[2] No maximum data was extracted for this compound.

[3] Results for this compound are based on lipid data.

Contaminants exceeding "generic" screening level in whole fish data

For contaminants without an EPA RfD, EPA calculated a generic screening level using the most stringent RfD of the compounds found in fish tissue: 3×10^{-6} mg/kg-d. This resulted in a screening level was 0.00741 µg/g. The 12 analytes in Table 5 had concentrations in whole body tissue that exceeded the generic screening level. The table also shows which data type (average or maximum concentration) had a value that exceeded the screening level.

Table 5. Contaminants exceeding generic screening level in whole fish data

Analyte	Concentration type that exceeds the generic screening level
Amphetamine	Average concentration[1]
BDE-49	Maximum concentration[3]
BDE-100	Maximum concentration[3]
DBDPE (Decabromodiphenyl ethane) [1]	Average concentration[1]
Dechlorane 602 [2]	Average concentration[1]
Dechlorane 604 [2]	Average concentration[1]
Metformin	Average concentration[1]
Long-chain chlorinated paraffins	Maximum concentration[3]
PFDoA	Maximum concentration
PFUnA	Maximum concentration
Sertraline	Average concentration[1]
Sulfadimethoxine	Average concentration[1]

[1] No maximum data was extracted for this compound.

[2] Results for this compound are based on lipid data.

[3] No average data was extracted for this compound.

Contaminants exceeding "generic" screening level in shellfish data

For contaminants without an EPA RfD, EPA calculated a generic screening level using the most stringent RfD of the compounds found in fish and shellfish tissue: 3×10^{-6} mg/kg-d. This resulted in a screening level of 0.00741 µg/g. The analyte in Table 6 had concentrations in shellfish tissue that exceeded the generic screening level. The table also shows which data type (average concentration, maximum concentration, or both) had a value that exceeded the screening level.

Table 6. Contaminants exceeding generic screening level in shellfish data

Analyte	Concentration type that exceeds the generic screening level
Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)	Maximum concentration Average concentration

Results of Process

EPA is proposing to develop two lists of compounds based on available information:

1. *Contaminants to Monitor for Advisories*: The compounds on this list are found to occur in fish at levels of concern to human health and have toxicity information in the form of an EPA oral reference dose, ATSDR minimum risk level, or EPA cancer slope factor. Table 7 shows the new compounds EPA is proposing to add to its existing list (in 2000 Guidance) of recommended compounds to monitor for fish advisories based on the process described in this document.
2. *Contaminants to Monitor to Watch*: The compounds on this list are those that may need advisories in the future. They are on the list because they have documented concentrations in fish and/or shellfish that could be of concern for human health, based on the generic screening level used in these analyses, but the federal government has not yet developed toxicity values such as reference doses or cancer slope factors for them. Table 8 shows the compounds EPA has identified based on the process described in this document.

Contaminants to Monitor for Advisories

EPA proposes to add ten contaminants (five PFAS compounds, one cyanotoxin, two flame retardants, and two metals) to the Contaminants to Monitor for Advisories list in the 2000 Guidance; these are shown in Table 7. These compounds met the criteria of being documented in studies as occurring in edible tissue of consumed fish or shellfish species at a concentration that exceeds the screening level associated with the reference dose (for non-cancer effects) or cancer slope factor and cancer risk level (for cancer effects) and therefore is of concern for human health.

Table 7. New contaminants to monitor for advisories

Class	Analyte
PFAS	Perfluorodecanoic acid (PFDA) Perfluorohexane sulfonic acid (PFHxS) Perfluorononanoic acid (PFNA) Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS)
Cyanotoxins	Microcystins
Flame retardants	BDE-47 BDE-99
Metals	Lead Thallium

Contaminants to Monitor to Watch

EPA proposes to add twenty-one contaminants (two cyanotoxins, five flame retardants, seven PFAS compounds, four pharmaceuticals, and three divisions of chlorinated paraffins) to a newly created Contaminants to Monitor to Watch list; these are shown in Table 8. These compounds

met the criteria of being documented in studies as occurring in edible tissue of consumed fish or shellfish species at a concentration that could be of concern for human health, based on the generic screening level used in these analyses. These compounds do not currently have government-issued reference doses or cancer slope factors. After the relevant toxicity values are developed, these compounds should be re-evaluated to determine if they warrant inclusion on consumption advisories.

Table 8. Contaminants to monitor to watch

Class	Analyte
Cyanotoxins	BMAA (β-methylamino-L-alanine) DABA (2,4-diaminobutyric acid dihydrochloride)
Flame retardants	BDE-49 BDE-100 Decabromodiphenyl ethane (DBDPE) Dechlorane 602 Dechlorane 604
PFAS	Perfluorodecanesulfonic acid (PFDS) Perfluorododecanoate (PFDoA) Perfluorooctanesulfonamide (PFOSA) Perfluorotetradecanoic acid (PFTeDA) Perfluorotridecanoate (PFTrDA) Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA) Perfluoro-2-propoxypropanoic acid (PFPrOPrA)
Pharmaceuticals	Amphetamine Metformin Sertraline Sulfadimethoxine
Other	Long-chain chlorinated paraffins Medium-chain chlorinated paraffins Short-chain chlorinated paraffins

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Appendix

Table A-1 shows the set of contaminants that EPA recommends state, tribal, and territorial fish advisory programs to monitor in its 2000 version of Volume 1 of *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories*.

Table A-1. Analytes Recommended for Monitoring in EPA's 2000 Guidance

Metals	Arsenic (inorganic) Cadmium Mercury (methylmercury) Selenium Tributyltin
Organochlorine Pesticides	Chlordane, total (cis- and trans-chlordane, cis- and trans-nonachlor, oxychlordane) DDT, total (2,4'-DDD, 4,4'-DDD, 2,4'-DDE, 4,4'-DDE, 2,4'-DDT, 4,4'-DDT) Dicofol Dieldrin Endosulfan (I and II) Endrin Heptachlor epoxide Hexachlorobenzene Lindane (γ-hexachlorocyclohexane; γ-HCH) Mirex Toxaphene
Organophosphate Pesticides	Chlorpyrifos Diazinon Disulfoton Ethion Terbufos
Chlorophenoxy Herbicides	Oxyfluorfen
Polycyclic aromatic hydrocarbons (PAHs)	
Polychlorinated biphenyls (PCBs)	Total PCBs (sum of PCB congeners or Aroclor equivalents)
Dioxins/furans	

DDT = p,p'-dichlorodiphenyl trichloroethane

DDE = p,p'-dichlorodiphenyl dichloroethylene

DDD = dichlorodiphenyldichloro ethane

Table A-2 shows the contaminants that EPA compiled during the literature search with a weight of evidence score of 2 or more.

Table A-2. Initial List of Potential Analytes Based on Literature Search

Analyte	Analyte Classification
Azithromycin	Antibacterial, antibiotic, and antimicrobial compounds
Cefotiam	
Cefoxitin	
Ciprofloxacin	
Enrofloxacin	
Erythromycin	
ICON (active ingredient fipronil)	
Lincomycin	
Linezolid	
Norfloxacin	
Norfluoxetine	
Ofloxacin	
Roxithromycin	
Sulfadimethoxine	
Sulfamethoxazole	
Sulfaquinoxaline	
Triclocarban	
Triclosan	
Polybrominated biphenyls (PBBs)	Brominated compounds
1,3,6,8-Tetrabromocarbazole	Chlorinated compounds
1,3,6,8-Tetrachlorocarbazole	
1,3,6-Tribromocarbazole	
1,8-Dibromo-3,6-dichlorocarbazole	
1-Bromo-3,6-dichlorocarbaozle	
2,3,6,7-Tetrachlorocarbazole	
2,7-Dibromocarbazole	
3,6-Dibromocarbazole	
3,6-Dichlorocarbzole	
3-Bromocarbazole	
3-Chlorocarbazole	
Chlorobenzenes	
Chloronaphthalene, 1-	
Chloronaphthalene, 2-	
Medium chain chlorinated paraffins	
Polychlorinated biphenyls (PCBs)	
Polychlorinated naphthalenes (PCNs)	
β-methylamino-L-alanine (BMAA)	Cyanotoxins and neurotoxins
Cylindrospermopsin	

Analyte	Analyte Classification
Diaminobutyric acid dihydrochloride (DABA)	
Domoic acid	
Microcystins	
Saxitoxin	Cyanotoxins and neurotoxins
1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane (TBECH)	
BDE, deca-	
BDE, octa-	
BDE, penta-	
BDE-100	
BDE-119	
BDE-119+BDE-120	
BDE-126	
BDE-153 (Hexabromodiphenyl ether, 2,2',4,4',5,5')	
BDE-154	
BDE-155	
BDE-17+BDE-25	
BDE-180	
BDE-183	
BDE-197	
BDE-198	
BDE-203	
BDE-204	
BDE-206	
BDE-207	Flame retardants
BDE-208	
BDE-209 (Decabromodiphenyl ether)	
BDE-28	
BDE-28+BDE-33	
BDE-47 (Tetrabromodiphenyl ether, 2,2',4,4'-)	
BDE-49	
BDE-51	
BDE-66	
BDE-75	
BDE-77	
BDE-99 (Pentabromodiphenyl ether, 2,2',4,4',5-)	
Debrominated diphenyl ethers (De-BDEs)	
Dechlorane 602	
Dechlorane 603	
Dechlorane 604	
Dechlorane Plus	
Hexabromocyclododecane (HBCDs)	
Hexabromocyclododecane, alpha- (α-HBCDD)	

Analyte	Analyte Classification
Hexabromocyclododecane, beta- (β-HBCDD)	Flame retardants
Hexabromocyclododecane, gamma- (γ-HBCDD)	
Hexabromocyclododecane, Sum (HBCDD)	
Methoxylated brominated diphenyl ethers (MeO-BDE)	
Monohydroxylated Polybrominated Diphenyl Ethers (OH-PBDEs)	
Polybrominated diphenyl ethers (PBDEs)	
Tetrabromobisphenol A	
Androstenedione	Hormones
Estradiol, 17β-	
Estrone	
Norethindrone	
Testosterone	
Chlorinated paraffins	Industrial by-products
Naphthenic acids	
Octachlorostyrene	
Produced water	
Ammonia (NH3)	Inorganics
Bromine	
Calcium	
Chlorine	
Iodine	
Nitrate	
Nitrite	
Orthophosphate	
Rare earth elements	
Sulphate (SO2)	
Zinc chloride	
Dimethylarsinate (DMA)	Metabolites
Arsenobetaine	
Benzoylecgonine	
Desmethyldiltiazem	
Hydroxypyrene, 1-	
Aluminum	Metals
Antimony	
Barium	
Beryllium	
Boron	
Cadmium	
Cesium	
Chromium (III)	
Chromium (VI)	

Analyte	Analyte Classification
Cobalt	Metals
Copper	
Iron	
Lead	
Lithium	
Magnesium	
Manganese	
Molybdenum	
Nickel	
Potassium	
Radiocesium	
Rubidium	
Silver	
Sodium	
Strontium	
Thallium	
Tin	
Titanium	
Tungsten	
Uranium	
Vanadium	
Zinc	
Copper oxide nanoparticles (CuO NPs)	Nanoparticles
Nanoparticles	
Zinc oxide nanoparticles (ZnO NPs)	
Radionuclides	Other
Semivolatile organic compounds (SVOCs)	
SSCP	
Trinitrotoluene, 2,4,6- (TNT)	
Aroclor 1016	PCBs
Aroclor 1254	
Cyclic volatile methyl siloxanes (cVMS)	Personal care products
Hexamethyldisiloxane (HMDS)	
Linear alkylbenzenes (LABs)	
Octamethylcyclotetrasiloxane (D4)	
Aldrin	Pesticides
Atrazine	
Benzene hexachloride, alpha-	
Benzene hexachloride, beta-	
Copper pyrithione (CuPT)	
Hexachlorobenzene (HCB)	
Isodrin	

Analyte	Analyte Classification
Methoxychlor	Pesticides
Methylarsonate (MA)	
Monomethylarsonic acid (MMA)	
Monosodium methanearsonate	
N,N-Diethyl-meta-toluamide (DEET)	
Rhothane (TDE)	
Telodrin	
Thiabendazole	
Triphenyltin	
Perfluoro-2-propoxypropanoic acid (PFPrOPrA)	PFAS
Pentafluorobenzoic acid (PFBA)	
Perfluorobutane sulfonate (PFBS)	
Perfluorodecane sulfonate (PFDS)	
Perfluorodecanoate (PFDA)	
Perfluorododecanoate (PFDoA)	
Perfluoroheptanesulfonic acid (PFHpS)	
Perfluoroheptanoate (PFHpA)	
Perfluorohexane sulfonate (PFHxS)	
Perfluorohexanoate (PFHxA)	
Perfluorononanoate (PFNA)	
Perfluorooctane sulfonate (PFOS)	
Perfluorooctanesulfonamide (PFOSA)	
Perfluorooctanoate (PFOA)	
Perfluoropentanoate (PFPA)	
Perfluoropentanoic acid (PFPeA)	
Perfluorotetradecanoate (PFTA)	
Perfluorotetradecanoic acid (PFTeDA)	
Perfluorotridecanoate (PFTrDA)	
Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)	
Albuterol	Pharmaceuticals
Alprazolam	
Amitriptyline	
Amlodipine	
Amphetamine	
Atenolol	
Atorvastatin	
Benztropine	
Caffeine	
Carbamazepine	
Cimetidine	
Clarithromycin	
Cocaine	

Analyte	Analyte Classification
Codeine	Pharmaceuticals
Cotinine	
Diazepam	
Diclofenac	
Diltiazem	
Dimethylxanthine	
Diphenhydramine, 1,7-	
Enalapril	
Fluoxetine	
Furosemide	
Gemfibrozil	
Glyburide	
Hydrochlorothiazide	
Hydrocodone	
Ibuprofen	
Meprobamate	
Metformin	
Metoprolol	
Miconazole	
Naproxen	
Nifedipine (Dehydro)	
Norverapamil	
Oxycodone	
Paroxetine	
Promethazine	
Propoxyphene	
Propranolol	
Ranitidine	
Sertraline	
Simvastatin	
Triamterene	
Trimethoprim	
Valsartan	
Verapamil	

Table A-3 shows the potential contaminants with a weight of evidence score or 2 or more and fillet data that EPA could extract from the literature.

Table A-3. List of Potential Analytes with Fillet Data

Classification	Analyte
Antibiotics	Sulfaquinoxaline
Flame retardants	BDE-100
	BDE-153 (Hexabromodiphenyl ether, 2,2',4,4',5,5')
	BDE-154
	BDE-155
	BDE-209 (Decabromodiphenyl ether)
	BDE-47 (Tetrabromodiphenyl ether, 2,2',4,4'-)
	BDE-49
	BDE-66
	BDE-99 (Pentabromodiphenyl ether, 2,2',4,4',5-)
	Dechlorane 602
	Dechlorane 603
	Dechlorane 604
	HBCDD, alpha- (Hexabromocyclododecane)
	HBCDD, beta-
	HBCDD, gamma-
	Tetrabromobisphenol - A (TBBP-A)
Cyanotoxins and neurotoxins	BMAA (β-methylamino-L-alanine)
	Cylindrospermopsin
	DABA (2,4-diaminobutyric acid dihydrochloride)
	Microcystins
Metals	Lead
	Nickel
	Thallium
PFAS	Pentafluorobenzoic acid (PFBA)
	Perfluorobutane sulfonate (PFBS)
	Perfluorodecanesulfonic acid (PFDS)
	Perfluorodecanoic acid (PFDA)
	Perfluorododecanoate (PFDoA)
	Perfluoroheptanesulfonic acid (PFHpS)
	Perfluoroheptanoate (PFHpA)
	Perfluorohexane sulfonate (PFHxS)
	Perfluorohexanoate (PFHxA)
	Perfluorononanoate (PFNA)
	Perfluorooctane sulfonate (PFOS)
	Perfluorooctanesulfonamide (PFOSA)
	Perfluorooctanoic acid (PFOA)

Classification	Analyte
	Perfluoropentanoic acid (PFPeA)
	Perfluorotetradecanoic acid (PFTeDA)
	Perfluorotridecanoate (PFTrDA)
	Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)
	Perfluoro-2-propoxypropanoic acid (PFPrOPrA)
Other	Medium chain chlorinated paraffins
	Radiocesium
	Short chain chlorinated paraffins

Table A-4 shows the potential contaminants with a weight of evidence score or 2 or more and whole body data that EPA could extract from the literature.

Table A-4. List of Potential Analytes with Whole Fish Data

Classification	Analyte
Antibacterial, antibiotic, and antimicrobial compounds	Azithromycin
	Erythromycin
	Norfluoxetine
	Sulfadimethoxine
	Triclocarban
	Triclosan
Flame retardants	BDE-100
	BDE-153 (Hexabromodiphenyl ether, 2,2',4,4',5,5')
	BDE-154
	BDE-155
	BDE-47 (Tetrabromodiphenyl ether, 2,2',4,4'-)
	BDE-49
	BDE-66
	BDE-75
	BDE-99 (Pentabromodiphenyl ether, 2,2',4,4',5-)
	Chlordene Plus
	DBDPE (Decabromodiphenyl ethane)
	Dechlorane 602
	Dechlorane 604
	HBB (Hexabromobiphenyl)
	HBCDD, beta-
	HBCDD, gamma-
	PBEB (pentabromoethylbenzene)
	Syn-Dechlorane plus
Metals	Lead
PFAS	Perfluorobutane sulfonate (PFBS)

Classification	Analyte
PFAS	Perfluorodecanoic acid (PFDA)
	Perfluorododecanoate (PFDoA)
	Perfluoroheptanoate (PFHpA)
	Perfluorohexane sulfonate (PFHxS)
	Perfluorohexanoate (PFHxA)
	Perfluorononanoate (PFNA)
	Perfluorooctane sulfonate (PFOS)
	Perfluorooctanesulfonamide (PFOSA)
	Perfluorooctanoic acid (PFOA)
	Perfluorotetradecanoic acid (PFTeDA)
	Perfluorotridecanoate (PFTrDA)
	Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)
Pharmaceuticals	Alprazolam
	Amitriptyline
	Amlodipine
	Amphetamine
	Diazepam
	Diltiazem
	Diphenhydramine, 1,7-
	Fluoxetine
	Gemfibrozil
	Metformin
	Miconazole
	Norverapamil
	Ranitidine
	Sertraline
	Verapamil
Other	Long-chain chlorinated paraffins

Table A-5 shows the potential contaminants with a weight of evidence score or 2 or more and shellfish data that EPA could extract from the literature.

Table A-5. List of Potential Analytes with Shellfish Data

Classification	Analyte
Cyanotoxins and neurotoxins	Microcystins
PFAS	Perfluorobutane sulfonate (PFBS)
	Perfluorodecanesulfonic acid (PFDS)
	Perfluorodecanoic acid (PFDA)
	Perfluorododecanoate (PFDoA)
	Perfluoroheptanoic acid (PFHpA)
	Perfluorohexane sulfonate (PFHxS)
	Perfluorohexanoate (PFHxA)
	Perfluorononanoate (PFNA)
	Perfluorooctane sulfonate (PFOS)
	Perfluorooctanoic acid (PFOA)
	Perfluorotetradecanoic acid (PFTeDA)
	Perfluorotridecanoate (PFTrDA)
	Perfluoroundecanoate (PFUdA, PFUnA, PFUnDA)

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EXTERNAL PEER REVIEW OF THE PROCESS FOR SELECTING CONTAMINANTS TO MONITOR IN FISH ADVISORY PROGRAMS

FINAL PEER REVIEW SUMMARY REPORT

October 2023

Submitted to:
U.S. Environmental Protection Agency
Office of Water, Office of Science and Technology
Standards and Health Protection Division
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Washington, DC 20460

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CONTENTS

1.0 INTRODUCTION

This report documents the results of an independent external peer review of the U.S. Environmental Protection Agency's (EPA) draft *Process for Selecting Contaminants to Monitor in Fish Advisory Programs*.

ERG, Inc. (a contractor to EPA) organized this review and developed this report. The report provides background on the development of the draft document (Section 1.1), describes ERG's peer reviewer selection process (Section 1.2), and provides reviewers' comments organized by charge question (Section 2.0) along with a summary of the comments by charge question. Appendix A provides the charge to reviewers and Appendix B presents the reviewer comments organized by reviewer.

1.1 Background

EPA developed the *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* (EPA, 2000) to help state, local, regional, and tribal environmental and public health officials who are responsible for developing and managing fish consumption advisories. This guidance, which consists of four volumes, is intended to be used together, since no single volume addresses all the topics involved in the development of fish consumption advisories. This four-volume guidance set includes:

- Volume 1: Fish Sampling and Analysis
- Volume 2: Risk Assessment and Fish Consumption Limits
- Volume 3: Overview of Risk Management
- Volume 4: Risk Communication

EPA is revising Volumes 1 and 2 to include changes that have occurred since these documents were published. These changes include, but are not limited to, contaminants of concern in fish, sampling design approaches, and default values for developing fish consumption limits. Descriptions of each volume can be found at: https://www.epa.gov/fish-tech/epa-guidance-developing-fish-advisories.

The purpose of this peer review was to review the proposed changes to the target analyte list found in Volume 1, Fish and Sampling Analysis. Reviewers were asked to evaluate the approach and process used for updating and selecting target analytes for use in screening studies by state, territorial and tribal fish advisory programs.

1.2 Peer Reviewers

For this review, ERG identified, screened, and selected reviewers who had no conflict of interest in performing the review, who are nationally recognized technical experts, and who had experience in one or more of the following disciplines:

- Toxicology
- Risk Assessment
- Analytical Chemistry

ERG initiated a search process, asking interested candidates to describe their qualifications and respond to a series of "Conflict of Interest" (COI) analysis questions. ERG carefully screened submissions to identify a pool of qualified, COI-free candidates. From the set of candidates who met the criteria, ERG proposed a pool of five candidates to EPA on September 12, 2023. From this pool, ERG selected three experts who collectively best met the selection criteria. ERG contracted with two and committed the following three experts to perform the review:

1. **Philip Goodrum, Ph.D., DABT**; Principal Toxicologist, GSI Environmental
2. **Gloria Post, Ph.D., DABT**; Research Scientist, New Jersey Department of Environmental Protection
3. **Penelope Rice, Ph.D., DABT**; Toxicologist and Subject Matter Expert, US Food and Drug Administration (no fee)

ERG provided reviewers with instructions, the draft document entitled *Process for Selecting Contaminants to Monitor in Fish Advisory Programs*, and the charge to reviewers (Appendix A of this report) prepared by EPA. Reviewers worked individually to develop written comments in response to the charge questions. After receiving reviewer comments, ERG compiled responses and prepared a summary of comments by charge question (see Section 2.0) and included the responses and requested clarifications from EPA organized by reviewer (see Appendix B).

2.0 SUMMARY OF REVIEWER COMMENTS ORGANIZED BY CHARGE QUESTION

This section summarizes reviewer comments by charge question. Each summary is followed by a table presenting individual reviewer responses to that charge question (see Appendix B for the complete set of reviewer comments).

2.1 Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?

All three reviewers agreed that the process EPA followed was reasonable, but also indicated that the process would benefit from some revision. One reviewer suggested incorporating toxicity values from databases less focused on North America. Two reviewers noted that using a cancer slope factor as a screening level for lead is highly unusual; both suggested that EPA's Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) model or EPA's Adult Lead Model should be used to develop a generic screening level. One reviewer recommended that the draft IRIS RfD values for PFHxS (released after the peer review document was written) and PFNA (when available) be used for calculating the screening levels for those compounds.

For calculating a generic screening level for contaminants without established toxicity information, all three reviewers questioned the use of the chronic reference value based upon the PFNA minimal risk level (MRL) produced by the Agency for Toxic Substances and Disease Registry (ATSDR). One reviewer stated that EPA should use a well-established toxicity value with a high degree of scientific consensus regarding the validity of the value and how it was derived. This reviewer commented this was not the case for PFNA, because IRIS is developing a draft assessment for it. Another reviewer stated that the generic screening level based on the ATSDR MRL for PFNA is highly uncertain and that ATSDR MRLs are based on animal data, not human data. This reviewer also asked if the generic screening level would be changed after the final IRIS assessment for PFDA is released since IRIS' RfD for PFDA would presumably be lower than ATSDR's value for PFNA. The third reviewer expressed that extrapolating the same reference dose across chemical classes seems unnecessary when it is possible to choose the lowest RfD within each chemical class.

One reviewer suggested updating the screening level equation to better reflect current state practices for implementing fish advisories. This reviewer also noted that, for occurrence data, sample maximums are very unreliable statistics and recommended using a high percentile (e.g., 95^{th} or 99^{th} percentiles) to represent high data values more appropriately. The same reviewer also recommended against using lipid-normalized concentrations and suggested that these values be converted to wet weight concentrations.

Reviewer	Comments
Reviewer 1	The EPA's process for compiling the preliminary contaminant list appears reasonable, although it is unclear why nanoparticles are included in the list. The databases which were mined for toxicity values for their contaminant list appear to be heavily focused on North America. The European Food Safety Authority (https://www.efsa.europa.eu/en/data-report/chemical-hazards-database-openfoodtox) and the World Health Organization (https://apps.who.int/food-additives-contaminants-jecfa-database/) have also published toxicity values for various contaminants found in food. This reviewer suggests that these databases also be included in EPA's review process, as this may broaden the chemical space covered by established toxicity values. The derivation of screening levels for contaminants with toxicity values (both non-cancer and cancer values) appears appropriate. However, this reviewer does not consider the EPA's 'generic screening level' appropriate. IRIS' assessment, and the associated lifetime/subchronic oral RfD value for PFNA exposure which forms the basis for the generic screening level, is still in draft. In commenting on the draft IRIS assessment, this reviewer pointed out inconsistencies in the selection of critical endpoint and derivation of the RfD for PFNA. A generic screening value for use in the risk assessment of a broad chemical space should be based on a well-established toxicity value with a high degree of scientific consensus regarding the validity of the value and how it was derived. This reviewer suggests that the EPA select another toxicity value on which to base their generic screening level.
Reviewer 2	As noted in the review document, the EPA (2000) *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* does not include all contaminants found in fish and shellfish that are currently of concern. For this reason, a process is needed to identify additional contaminants that should be monitored in aquatic organisms and considered for consumption advisory development, and EPA presents this process in the review document. The process followed by EPA likely identified most contaminants that have been detected In U.S. fish and/or shellfish at levels that might warrant fish consumption advisories. However, some aspects of the this process should be clarified, as noted in my comments below: • p. 2, first paragraph. Suggest clarifying whether all states, tribes, and territories must have and/or actually have fish and shellfish advisory programs, or whether this is optional and/or only some states have such programs. • p. 2, Background section, numbered points. Points 2 and 3 are not meaningful as written because "persistent" and "bioaccumulative" are not quantitatively defined. Importantly, the degree of persistence and bioaccumulation needed for a contaminant to reach a concentration of human health concern in aquatic organisms is dependent on the dose at which toxicity occurs. Contaminants with very low non-cancer or cancer screening levels can accumulate to levels of concern even if they are not highly persistent or highly bioaccumulative. It is suggested that this issue be addressed by adding the word "sufficiently" to points 2 and 3, as shown in **bold** below. Relevant to this suggestion, point 1 already includes the word "sufficient" regarding the quantity released to the environment.

Reviewer	Comments
	Suggested revisions: 1. The compound must be **sufficiently** persistent in water and/or air for transport in the environment once released. 2. The chemical nature of the substance must cause it to bioaccumulate **sufficiently** in food webs due to an affinity for fish tissues, which vary both by chemical and fish species characteristics. • p. 3, first full paragraph on bioaccumulation. Related to the comment on bioaccumulation above, this paragraph should state that the degree of bioaccumulation needed for a contaminant to post a risk to consumers depends on the concentration of the contaminant found in the aquatic environment (e.g., water, sediment) and the concentration of the contaminant in aquatic organisms that results in a human health risk from consumption of the organism. In other words, a contaminant that is not highly bioaccumulative can be present in aquatic organisms at levels of concern for consumers' consumption if it is present in the aquatic environment (water, sediments) at a high enough concentration and/or if toxicity can occur from very low doses. • p. 3, second full paragraph, second sentence. "Reproductive, developmental (including neurodevelopmental), hepatotoxic (liver), and immunotoxic are among the most common types of human health effects from exposure to contaminants in fish." The sentence should be revised either to say that these are among the most common types of <u>non-cancer</u> human health effects or to add carcinogenicity to the list of health effects. • p. 4, second set of numbered points in *Pre-Search Definition of Screening Criteria* section. Regarding points 2 and 3, it is unclear how "potential to bioaccumulate," "prevalent…in the environment," and "persistent in the environment" are defined for use as criteria. Relevant to comments above, the magnitude of prevalence, persistence, and bioaccumulation necessary for a contaminant in fish or shellfish to pose a human health risk from consumption is dependent on the dose at which toxicity can occur. Additionally, regarding point 5, please note that ATSDR develops minimal risk levels (MRLs), not reference doses, for non-cancer effects, and ATSDR does not develop cancer slope factors or other toxicity factors for carcinogenic effects. • p. 4, *Article Inclusion Criteria* section. "Published in 2000 or later (to capture information published after the 2000 Guidance)." A minor comment is that the literature search for the 2000 Guidance likely ended prior to 2000, since it took time for development and review of a document prior to the date when it was finalized. Does the 2000 Guidance include the date when the literature search that was used was performed? • p. 5, *Keywords.* The literature search strategy (e.g., how AND, OR, etc. were used with the keywords listed) should be provided. Additionally, does "states" mean "state environmental agencies," and how were the states listed selected? Were publications by the Delaware River Basin Commission (DRBC) and other similar interstate authorities (e.g., Ohio River Valley Water Sanitation Commission [ORSANCO])

Reviewer	Comments
	included? DRBC has conducted multiple studies of emerging contaminants in fish, including pharmaceuticals, flame retardants, PFAS, and others. See https://www.nj.gov/drbc/programs/quality/cecs.html. • p. 5, *Weight of evidence analysis.* The weight of evidence approach, based on the information presented here, does not appear to be completely logical and supportable. Specifically, one of the four criteria used to assign points is "species found in the U.S." However, the *Overview* section (p. 1) says that articles that contained "fish not found in U.S. waters" were removed. Based on this statement, it appears that all articles that were included contained information on species of fish found in the U.S. However, this is inconsistent with the weight of evidence discussion (p. 5), in which it appears that a paper would be included even if it was not assigned 1 point for "species found in the U.S." if it was assigned 2 points for meeting two other criteria. Additionally, it is unclear how a study could meet the criterion for including "BCF or BAF data" without also meeting the criterion for including "information on the contaminant's detection in fish." Furthermore, even if a study provided a BCF or BAF for a contaminant without contaminant concentration data, the study would have been removed, since it is stated in first full paragraph of p. 7 that "EPA removed compounds without concentration data…". Based on the above, it appears that all included studies would have met the following two criteria: including "information on the contaminant's detection," and including information on "species found in the U.S." Also, the criterion for "oral toxicity data" is unclear. Does this mean data from studies of oral toxicity in mammalian species, or does this mean an oral toxicity factor (e.g., reference dose, cancer slope factor)? • p. 7, *Researched Toxicity Values* section. The review document does not mention that the process used for selection of the toxicity values in the review document differs from the process used by in the EPA (2015) that is cited, and clarification of this issue needs to be added. Specifically, while the list of eight sources of toxicity values in the review document is the same as the list used by EPA (2015), the process for selection of the toxicity factor in the review document is not the same as in EPA (2015). In the review document, toxicity values were selected from the eight sources listed based on the order in which the source is listed (i.e., when toxicity values were available from multiple sources, the toxicity value from the source highest on the list was used). In contrast, EPA (2015) used a different process to select from among the available toxicity factors. The description of this process is included in each of the contaminant-specific " Update of Human Health Ambient Water Quality Criteria" documents (linked from the table of human health criteria at https://www.epa.gov/wqc/national-recommended-water-quality-criteria-human-health-criteria-table; for example, see https://www.epa.gov/sites/default/files/2015-10/documents/final-1-1-1-trichloroethane.pdf) and is copied below:

Reviewer	Comments
	"After identifying and documenting all available toxicity values, EPA followed a systematic process to select the toxicity values used to derive the AWQC for noncarcinogenic and carcinogenic effects. EPA selected IRIS toxicity values to derive the updated AWQC if any of the following conditions were met: 1. EPA's IRIS toxicological assessment was the only available source of a toxicity value. 2. EPA's IRIS toxicological assessment was the most current source of a toxicity value. 3. EPA's IRIS program was reassessing the chemical in question and had published the draft Toxicological Review for public review and comment, discussion at a public meeting, and subsequent expert peer review. 4. The toxicity value from a more current toxicological assessment from a source other than EPA IRIS was based on the same principal study and was numerically the same as an older EPA IRIS toxicity value. 5. A more current toxicological assessment from a source other than EPA IRIS was available, but it did not include the relevant toxicity value (chronic-duration oral RfD or CSF). 6. A more current toxicological assessment from a source other than EPA IRIS was available, but it did not introduce new science (e.g., the toxicity value was not based on a newer principal study) or use a more current modeling approach compared to an older EPA IRIS toxicological assessment. EPA selected the toxicity value from a peer-reviewed, publicly available source other than EPA IRIS to derive the updated AWQC if any of the following conditions were met: 1. The chemical is currently used as a pesticide, and EPA Office of Pesticide Programs had a toxicity value that was used in pesticide registration decision-making. 2. A toxicological assessment from a source other than EPA IRIS was the only available source of a toxicity value. 3. A more current toxicological assessment from a source other than EPA IRIS introduced new science (e.g., the toxicity value was based on a newer principal study) or used a more current modeling approach compared to an older EPA IRIS toxicological assessment." • p. 7, *Researched Toxicity Values* section. The hotlinks in this section of the review document do not work. It is assumed that this will be fixed in the final version. • p. 7, *Researched Toxicity Values* section, toxicity values for PFAS. The toxicity values for PFNA and PFHxS referred to as "reference doses" from the proposed EPA (2023) National Primary Drinking Water Regulation (NPDWR) are called "chronic reference values" not "reference doses." The proposed rule states that, for PFNA and PFHxS, "a

Reviewer	Comments
	chronic reference value based on an Agency For Toxic Substances And Disease Registry (ATSDR) intermediate-duration oral Minimal Risk Level" was developed. A draft IRIS reference dose for PFHxS is now available, and a draft IRIS reference dose for PFNA will be released soon. Since the draft IRIS PFDA value is used in the review document, it is suggested that the draft IRIS PFHxS value (and the draft IRIS PFNA values, when available), which are more recent than the ATSDR/NPDWR values, also be used. Relevant to this point, a key difference between the recent reference doses for long-chain PFAS developed by EPA (Office of Water – PFOA, PFOS; IRIS – PFDA, PFHxS) and the ATSDR Minimal Risk Levels for long-chain PFAS (PFOA, PFOS, PFNA, PFHxS) is that the EPA toxicity values are based on human data, and they are much more stringent than the ATSDR values based on animal data. • p. 7, *Screening Level Calculations and Analysis,* general comment. For contaminants with a very low Reference Dose or a high cancer potency (slope factor), general dietary exposure in the general population may exceed the exposure from consumption of a weekly fish meal at the screening concentration. In such cases, it is not beneficial from a public health viewpoint to issue a fish consumption advisory based on the screening concentration because other foods that do not have the health benefits associated with fish will be consumed instead of fish, while exposure to the contaminant will still be above the toxicity value. This situation is much more likely to occur if fish consumption advisories for carcinogens are based on the 10^{-6} risk level instead of the 10^{-5} risk level, as was done in the screening level calculations in the review document (p. 9). In such cases, alternative approaches for development of fish consumption advisories may be considered. For example, in New Jersey's development of fish consumption advisories for dioxins and related compounds, the lifetime cancer risk resulting from background dietary exposures to dioxin-like compounds was estimated to be about 10^{-3}. For this reason, an advisory based on 10^{-5} or 10^{-6} risk would not result in a reduction of risk from dioxins and related compounds. Therefore, the advisories were developed using an alternative approach based on comparison with background dietary exposures. For the general population, it was recommended that the fish consumption advisory be based on an intake of dioxin and related compounds equal to the daily background exposure in the total diet, such that consumption of fish at the advisory level would result in a doubling of the background exposure. The advisory for the high-risk population (pregnant and nursing mothers, women of childbearing age, and young children) considered the fact that consumption of fish is beneficial as part of a healthy diet. For this population, it was recommended that daily dioxin exposure from consumption of fish should not exceed twice the exposure of an average meal, and it was concluded that this exposure was likely to fall within the range of normal dietary variation. • p. 7, *Screening Level Calculations and Analysis.* It should be clarified in the text (not just in the equation and the footnote) that the screening values for the general population (adult and pregnant individual) developed in the review document are based on weekly consumption of one 8-ounce fish meal. This is important because the EPA (2000)

Reviewer	Comments
	guidance that is cited (Volume 2, Section 3) provides information for developing screening values based on several different consumption frequencies. • p. 8, last paragraph, "generic" screening level. It is recognized that a "generic" toxicity value for screening of contaminants for which no toxicity value is available is needed. Based on the bioaccumulative potential and low-dose toxicity of long-chain PFAS, it is likely that a toxicity value based on a long-chain PFAS such as PFNA will be protective for most other contaminants. That being said, the "generic" screening level based on a toxicity value of 3×10^{-6} mg/kg/day (based on the ATSDR MRL) for PFNA is highly uncertain. Additionally, it is stated that the "lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed)" was used for the generic screening value. However, as discussed above, IRIS is currently developing Reference Doses for several long-chain PFAS based on human data, and these IRIS Reference Doses are lower than the ATSDR MRLs based on animal data. It is likely that the draft IRIS toxicity assessment for PFDA, which includes a much lower Reference Dose than the ATSDR PFNA value used here, will be finalized soon. When this occurs, will the "generic" toxicity value be revised? For contaminants that do not have a toxicity value in the eight sources listed in the review document, chemical-specific toxicity values from other sources (e.g., values developed by state environmental or health agencies other than California EPA) could be reviewed and considered. It is stated in the section on *Researched Toxicity Values* that other sources were not used "because of the variability of methods applied and inconsistency of the existence of adequate quality control documentation." However, it is unlikely that chemical-specific values developed by states (e.g., New Jersey, Minnesota, Massachusetts) using EPA risk assessment guidance are more uncertain than a "generic" value based on the toxicity value for a different chemical. As one example, New Jersey has developed a Reference Dose of 1.3×10^{-6} mg/kg/day (1.3 ng/kg/day) for perfluoroundecanoic acid specifically for use in fish consumption advisories. See https://dep.nj.gov/wp-content/uploads/dsr/pfunda-fish-consumption-trigger.pdf. • Comments on screening levels in Excel spreadsheet: ○ In these spreadsheets, the concentration data in columns G, H, and I are shown in units of ng/g (which is ppb, although not stated) but the Screening Levels in the columns to the right are shown in units of µg/g (ppm). This inconsistency in units is confusing and may easily be overlooked by the reader, and consistent units should be used. ○ The Screening Level for lead is based on cancer risk using the CalEPA (2011) cancer slope factor because no Reference Dose is available for lead. The reason that there is no Reference Dose for lead is because there is no known threshold for the neurodevelopmental effects of lead in children, and these neurodevelopmental effects are generally the focus of concern regarding risks of lead exposure. If possible, development of a Screening Level and fish consumption advisory for lead that is

Reviewer	Comments
	protective for neurodevelopmental effects of lead in children, using the EPA Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) model, could be considered. New Jersey has used such an approach for its fish consumption advisories for lead. ○ The cancer slope factor for PFOA of 0.0293 mg/kg/day shown in the "fillet-analysis w tox info" and "shellfish-analysis w tox info" spreadsheets is incorrect. The cancer slope factor from the cited EPA (2023) reference is 0.0293 **ng/kg/day**, which is 29,300 mg/kg/day. ○ The cancer slope factors for PFOA and PFOS are missing from the "WholeBody-analysis w tox info" spreadsheet.
Reviewer 3	Yes, overall, the process EPA followed to identify priority compounds is reasonable. However, EPA might consider revising the documentation and analyte selection process in these areas: 1. Update the equations used to calculate screening levels (SLs) to more closely align with current fish advisory practices. The current equation cites to the 2000 guidance, which is a special case of a more general equation. 2. Provide more analysis and documentation of the fish tissue concentrations summarized from the literature, particular for analytes that are selected because the sample maximum concentrations exceeds the SL. 3. Consider providing different weighting factors to these two conditions: A. sample maximum > SL and sample mean ≤ SL B. sample maximum > SL and sample mean > SL 4. Consider refining the decision process for selecting an RfD to serve as a protective surrogate value when the RfD is missing for a chemical. 5. Derive a SL for lead (Pb) using EPA's lead risk models, rather than the cancer slope factor. 6. Either exclude the lipid-normalized concentrations, or apply a default assumption for lipid content to convert the values to wet weight units. The basis for each recommendation is provided below. **Screening Level (SL) Equations** Separate equations for calculating a fish tissue screening level (SL) are provided for noncancer and cancer endpoints. The equations are consistent with the 2000 Guidance, but could be updated to more clearly show the underlying assumptions and to reflect how states currently implement fish advisories. Applying abbreviations for convenience, the equation presented to calculate a screening level for noncancer effects (SL_{nc}) on p.7, including the unit conversion factor (CF) for mass discussed on p. 8, is: $$SL_{nc} = \frac{RfD \times BW}{CR \times CF} [=] \frac{\text{(mg COPC/kg BW-day)} \times \text{(kg BW)}}{\text{(g ww/day)} \times 0.001 \text{ kg/g}}$$

Reviewer	Comments
	where, SLnc = fish tissue concentration (mg/kg ww) RfD = chronic oral refence dose (mg/kg-day) BW = body weight (kg) CR = average daily fish consumption rate (g ww/day) CF = conversion factor (0.001 kg per g) What is implied, but not stated directly, is that the SL is the concentration that, when included in the calculation of average daily dose (ADD), equals the RfD. In other words, the ratio of the ADD/RfD is 1, or equivalently, the target hazard quotient (THQ) is 1. Also, in practice, most state agencies consider fish consumption rate to be the product of the meal size and meal frequency, which is how different meal frequencies are ultimately determined. Finally, some agencies also apply a relative source contribution (RSC) to account for additional exposure pathways that may contribute to a total average daily dose. Considering all of these concepts, a more general expression for SL is: $$SL_{nc} = \frac{THQ \times RfD \times RSC \times BW}{(MS \times MF) \times CF}$$ where, SLnc = fish tissue concentration (mg/kg ww) THQ = target hazard quotient RfD = chronic oral refence dose (mg/kg-day) RSC = relative source contribution BW = body weight (kg) MS = meal size (g ww/meal) MF = average daily meal frequency (meals/day) CF = conversion factor (0.001 kg per g) Then, it can be stated that two assumptions used in the SL are: 1) THQ =1 (which would open the door for some discussion on the science policy decision, and standard conventions used by USEPA in selecting a target level); and 2) RSC = 1 (which would also open the door for some discussion on why this is used in the SL derivation, but might be revisited in site-specific applications). The product of (MS x MF) is CR, and USEPA can continue to present the CR estimates for typical and high-end consumers, and briefly discuss what meal frequency these correspond to when expressed over a period of one month or one year. A similar general equation can be presented for the SL for cancer endpoints.

Reviewer	Comments
	Summary of Occurrence Data on Concentrations in Fish Tissue The guidance document discuss the literature review methods and data usability criterion. The occurrence data generated from this process are provided in the Excel file (Screen Level Calculations.xlsx), grouped into separate worksheets for: 1) fillet data; 2) whole body data; 3) shellfish data. The occurrence data are distilled down to two summary statistics – "Maximum" and "Average". The sample maximum is a very unstable summary statistic, and subject to extreme results that do not actually represent the conditions found in most water bodies in the United States. The chances of observing an extreme value actually increases with increasing sample sizes. It is clear that one of the reasons for selecting the maximum is that the choice of statistics is limited to a large extent by the information presented in table summaries in the literature – it is unreasonable to expect to obtain the underlying raw data from most published studies. However, a preferred (more stable) statistic, that achieves the goal of representing a high-end value, would simply be an upper percentile (e.g., 95th percentile, or even 99th percentile). A recommended hierarchy of summary statistics for representing a high-end value is: • Reported upper percentile (90th, 95th, or 99th) • Estimate of upper percentile based on an assumed distribution (e.g., mean and standard deviation are reported, so assume a lognormal distribution to estimate the corresponding 95th percentile) • Sample maximum The following extreme cases of sample maximums are noted by comparing the ratio of the sample maximum to the arithmetic mean: Worksheet | Chemical | Maximum (ng/g) | Average (ng/g) | Ratio of Max/Average Fillet | PFDoA | 859,000 | 4.2 | 204,135 Fillet | PFOS | 2,840,000 | 53.1 | 53,525 Whole Body | BDE-99 | 650 | 0.24 | 2,708 Given the unreliability of the sample maximum as an indicator of conditions on a national scale, the rather large set of analytes for which only a maximum is provided (there are no estimates of the mean) should be carefully considered, at least in terms of the weighting scores used to rank each analyte. The following counts of analytes for which no "average" is available are noted, by chemical class: Worksheet | Chemical Class | Number of Analytes Missing an Average Fillet | Flame Retardants | 16

Reviewer	Comments

	PFAS	12
	Metals	1
	Chlorinated	1
	Cyanotoxin	1
	Other (paraffins)	2
Whole Body	Flame Retardants	8
	PFAS	3
	Metals	1
	Other (paraffins)	1

The one metal listed in the table above is for lead. Lead is included in this guidance based on the cancer slope factor, which is an extremely unusual choice. From my experience as a toxicologist and frequent participant on EPA's science advisory panels involving lead, lead is not regulated based on the cancer slope factor at any site, for any medium. USEPA and state agencies rely instead on the screening levels developed from regulatory models that predict blood lead concentrations (e.g., IEUBK or Adult Lead Model) from average daily intake. The USEPA Regional Screening Level tool[1] and guidance notes, "EPA has no consensus RfD or SFO for inorganic lead, so it is not possible to calculate SLs as we have done for other chemicals". EPA should develop a generic fish tissue level using one of EPA's lead models. For example, alternative dietary inputs can easily be included in the IEUBK model for children to develop a protective SL for lead in fish tissue.

Consider also including the number of studies and the number of study values that were curated from the literature and used to derive the "Maximum" and "Average".

Do not include the tissue concentrations that are lipid normalized, directly in the comparison to the toxicity values. The units matter in this case. A preferred approach would be to apply a general assumption for % lipid content to convert the lipid-normalized values to wet weight concentrations. Or, alternatively, exclude the study results that are expressed only as lipid normalized values.

Surrogates RfD for Missing Values

EPA elected to the RfD for PFNA (3E-06 mg/kg-day) as the proxy value for analytes without an RfD because, "it is the lowest final RfD for all contaminants being considered for inclusion in the monitoring list". In the Excel file, these are listed as "generic SLs" and include chemicals from a wide range of categories: antibacterials and antibiotics, cyanotoxins, flame retardants, and pharmaceuticals. This extrapolation across chemical classes seems unnecessary when it is possible to select from the lowest RfD with the same chemical class.

[1] https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search

2.2 Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?

All three reviewers agreed that the list of contaminants is reasonable and comprehensive. One reviewer noted that there are other compounds of concern that could be included in the list, but that these contaminants are not well known or well researched; this reviewer indicated that the list is reasonable even without the additional contaminants. Another reviewer noted that some states have already developed fish consumption advisories for many contaminants on the list.

Reviewer	Comments
Reviewer 1	The EPA's list of contaminants reflects those chemicals which have been measured in fish in published studies. This list is only a subset of the actual contaminants that may be found in fish, as studies are generally only done on compounds which are widely known to be present in fish and/or are easy to analyze in fish tissue. It is likely that the EPA's list will fail to capture compounds, like metabolites of fluorotelomer sulfonates, which are not commonly the subject of scientific studies in the broader research community. However, there is little the EPA can do to remedy this issue, short of itself conducting a nontargeted analytical assessment of contaminants in a range of species from different geographic areas, which would be very time-consuming and expensive. Given the time- and resource limitations, the EPA's list is reasonable.
Reviewer 2	The list of contaminants to monitor for advisories in Table 7 appears reasonable. It should be noted that New Jersey and other states already have developed fish consumption advisories for many of the contaminants in Table 7. Of the chemicals included on this list, New Jersey has developed fish consumption advisory triggers and/or waterbody-specific fish consumption advisories for PFOA, PFOS, PNA, microcystins, and lead. Several other states have also developed fish consumption advisories for PFAS. California has also developed consumption trigger for microcystins, and other states may also have developed advisories for contaminants on this list. The list of contaminants to monitor to watch in Table 8 also appears to be reasonable.
Reviewer 3	Yes, the range of chemical classes makes sense and appears to be comprehensive. See above for recommendations on revisiting the approach used to derive SLs for some of these analytes.

2.3 Are there additional contaminants that should be included in the "monitor for advisories" list or "monitor to watch" list? If so, what are they, and why should they be included?

Two reviewers suggested including additional contaminants. One reviewer recommended adding 6:2 di- and mono-PAPs and fluorotelomer sulfonates to the lists, as they all have shown high bioconcentration factor (BCF) values in recent studies. Another reviewer suggested adding additional cyanotoxins, such as cylindrospermopsin, anatoxin-a, and saxitoxin to the lists, because harmful algal blooms (HABs) are of current concern. This reviewer noted that cyanotoxin advisories should take into account that HAB exposures are often short-term, not chronic.

Reviewer	Comments
Reviewer 1	This reviewer suggests including 6:2 di- and monoPAPs and fluorotelomer sulfonates in the candidate list, as fluorotelomer sulfonates have been previously shown to accumulate in marine invertebrates (https://pubs.acs.org/doi/10.1021/acs.est.9b00927) and both have had reportedly high BCF values in published studies (https://pubs.acs.org/doi/epdf/10.1021/acs.est.2c03734).
Reviewer 2	The list of additional contaminants in the "monitor for advisories" and "monitor to watch" lists include the contaminants identified through the process described in the review document. Inclusion of additional cyanotoxins (e.g., cylindrospermopsin, anatoxin-a, and/or saxitoxin) could be considered since potential risks from fish from waterbodies with harmful algal blooms (HABs) are of current concern. New Jersey and California have developed fish consumption triggers for cylindrospermopsin and anatoxin-a, and other states have developed qualitative advice for consumption of fish where HABs have occurred. Advisories for cyanotoxins should consider the fact that exposure to cyanotoxins in fish is likely to be short-term or subchronic, rather than chronic, due to the relatively short timeframe that a HAB persists in a waterbody.
Reviewer 3	I am not aware of any additional contaminants that would be reasonable candidates to include in the monitoring lists.

APPENDIX A

CHARGE TO REVIEWERS

Technical Charge to External Peer Reviewers

Contract GSA GS-00F-079CA; BPA #68HERH23A0019
Call Order 68HERH23F0356 (ERG Call Order 002)
September 2023

External Peer Review of the Process for Selecting Contaminants to Monitor in Fish Advisory Programs

BACKGROUND

EPA developed the Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories (EPA, 2000) to help state, local, regional and tribal environmental and public health officials (intended audience) who are responsible for developing and managing fish consumption advisories. This guidance which consists of four volumes is intended to be used together, since no single volume addresses all the topics involved in the development of fish consumption advisories. This four-volume guidance set includes:

- Volume 1: Fish Sampling and Analysis
- Volume 2: Risk Assessment and Fish Consumption Limits
- Volume 3: Overview of Risk Management
- Volume 4: Risk Communication

EPA is revising Volumes 1 and 2 to include changes that have occurred since these documents were published. These changes include but are not limited to contaminants of concern in fish, sampling design approaches, and default values for developing fish consumption limits. Descriptions of each volume can be found at: https://www.epa.gov/fish-tech/epa-guidance-developing-fish-advisories.

The objective of this peer review is to evaluate the approach and process used for updating and selecting contaminants that state, territorial and tribal fish advisory programs should monitor.

CHARGE QUESTIONS

1. Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?
2. Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?
3. Are there additional contaminants that should be included in the “monitor for advisories” list or “monitor to watch” list? If so, what are they, and why should they be included?

APPENDIX B

INDIVIDUAL REVIEWER COMMENTS AND CLARIFICATIONS

COMMENTS SUBMITTED BY

REVIEWER 1

External Peer Review of the Process for Selecting Contaminants to Monitor in Fish Advisory Programs

Charge Questions

1. **Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?**

   The EPA's process for compiling the preliminary contaminant list appears reasonable, although it is unclear why nanoparticles are included in the list. The databases which were mined for toxicity values for their contaminant list appear to be heavily focused on North America. The European Food Safety Authority (https://www.efsa.europa.eu/en/data-report/chemical-hazards-database-openfoodtox) and the World Health Organization (https://apps.who.int/food-additives-contaminants-jecfa-database/) have also published toxicity values for various contaminants found in food. This reviewer suggests that these databases also be included in EPA's review process, as this may broaden the chemical space covered by established toxicity values. The derivation of screening levels for contaminants with toxicity values (both non-cancer and cancer values) appears appropriate. However, this reviewer does not consider the EPA's 'generic screening level' appropriate. IRIS' assessment, and the associated lifetime/subchronic oral RfD value for PFNA exposure which forms the basis for the generic screening level, is still in draft. In commenting on the draft IRIS assessment, this reviewer pointed out inconsistencies in the selection of critical endpoint and derivation of the RfD for PFNA. A generic screening value for use in the risk assessment of a broad chemical space should be based on a well-established toxicity value with a high degree of scientific consensus regarding the validity of the value and how it was derived. This reviewer suggests that the EPA select another toxicity value on which to base their generic screening level.

2. **Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?**

   The EPA's list of contaminants reflects those chemicals which have been measured in fish in published studies. This list is only a subset of the actual contaminants that may be found in fish, as studies are generally only done on compounds which are widely known to be present in fish and/or are easy to analyze in fish tissue. It is likely that the EPA's list will fail to capture compounds, like metabolites of fluorotelomer sulfonates, which are not commonly the subject of scientific studies in the broader research community. However, there is little the EPA can do to remedy this issue, short of itself conducting a nontargeted analytical assessment of contaminants in a range of species from different geographic areas, which would be very time-consuming and expensive. Given the time- and resource limitations, the EPA's list is reasonable.

3. **Are there additional contaminants that should be included in the "monitor for advisories" list or "monitor to watch" list? If so, what are they, and why should they be included?**

   This reviewer suggests including 6:2 di- and monoPAPs and fluorotelomer sulfonates in the candidate list, as fluorotelomer sulfonates have been previously shown to accumulate in marine invertebrates

(https://pubs.acs.org/doi/10.1021/acs.est.9b00927) and both have had reportedly high BCF values in published studies (https://pubs.acs.org/doi/epdf/10.1021/acs.est.2c03734

Requested Clarification from EPA

Question for Reviewer 1:

You suggested that the EPA select another toxicity value on which to base the generic screening level. EPA did not use the draft IRIS PFNA reference dose in its generic screening level calculation, because IRIS has not released the draft assessment yet and because draft values can change. The calculation used ATSDR's final oral MRL for PFNA from 2021. Using the lowest developed RfD (4 x 10-10 mg/kg-d, IRIS' draft RfD for PFDA) results in such a low screening level that detection at any concentration would result in a contaminant being added to the list. What toxicity value would you suggest that EPA use when calculating the generic screening level?

Reviewer 1 Response:

I don't think it is appropriate to use any given compound's specific value as a generic screening value for any contaminant without data in the absence of consideration of the structural relatedness of the data-poor contaminant to the reference chemical. Instead, I would advise that EPA to take a case-by-case approach to the development of screening levels for data-poor compounds. This assessment should assess the structural similarity of a data-poor contaminant with contaminants that have specific screening values. If the data-poor contaminant is structurally-similar to a compound with a data-based screening value, the structural analog's screening value may be applied to the assessment of exposure to the data-poor compound. Alternatively, high throughput NAMs may be used to identify toxicologically-similar index chemicals whose screening value would be appropriate for use in the risk assessment of exposure to a data-poor chemical.

COMMENTS SUBMITTED BY

REVIEWER 2

External Peer Review of the Process for Selecting Contaminants to Monitor in Fish Advisory Programs

Charge Questions

1. **Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?**

   Response: As noted in the review document, the EPA (2000) *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories* does not include all contaminants found in fish and shellfish that are currently of concern. For this reason, a process is needed to identify additional contaminants that should be monitored in aquatic organisms and considered for consumption advisory development, and EPA presents this process in the review document.

   The process followed by EPA likely identified most contaminants that have been detected in U.S. fish and/or shellfish at levels that might warrant fish consumption advisories. However, some aspects of the this process should be clarified, as noted in my comments below:

   - p. 2, first paragraph. Suggest clarifying whether all states, tribes, and territories must have and/or actually have fish and shellfish advisory programs, or whether this is optional and/or only some states have such programs.
   - p. 2, Background section, numbered points. Points 2 and 3 are not meaningful as written because "persistent" and "bioaccumulative" are not quantitatively defined. Importantly, the degree of persistence and bioaccumulation needed for a contaminant to reach a concentration of human health concern in aquatic organisms is dependent on the dose at which toxicity occurs. Contaminants with very low non-cancer or cancer screening levels can accumulate to levels of concern even if they are not highly persistent or highly bioaccumulative. It is suggested that this issue be addressed by adding the word "sufficiently" to points 2 and 3, as shown in **bold** below. Relevant to this suggestion, point 1 already includes the word "sufficient" regarding the quantity released to the environment.

     Suggested revisions:

     1. The compound must be **sufficiently** persistent in water and/or air for transport in the environment once released.
     2. The chemical nature of the substance must cause it to bioaccumulate **sufficiently** in food webs due to an affinity for fish tissues, which vary both by chemical and fish species characteristics.

   - p. 3, first full paragraph on bioaccumulation. Related to the comment on bioaccumulation above, this paragraph should state that the degree of bioaccumulation needed for a contaminant to post a risk to consumers depends on the concentration of the contaminant found in the aquatic environment (e.g., water, sediment) and the concentration of the contaminant in aquatic organisms that results in a human health risk from consumption of the organism. In other words, a contaminant that is not highly

bioaccumulative can be present in aquatic organisms at levels of concern for consumers' consumption if it is present in the aquatic environment (water, sediments) at a high enough concentration and/or if toxicity can occur from very low doses.

- p. 3, second full paragraph, second sentence. "Reproductive, developmental (including neurodevelopmental), hepatotoxic (liver), and immunotoxic are among the most common types of human health effects from exposure to contaminants in fish." The sentence should be revised either to say that these are among the most common types of non-cancer human health effects or to add carcinogenicity to the list of health effects.
- p. 4, second set of numbered points in *Pre-Search Definition of Screening Criteria* section. Regarding points 2 and 3, it is unclear how "potential to bioaccumulate," "prevalent…in the environment," and "persistent in the environment" are defined for use as criteria. Relevant to comments above, the magnitude of prevalence, persistence, and bioaccumulation necessary for a contaminant in fish or shellfish to pose a human health risk from consumption is dependent on the dose at which toxicity can occur.

  Additionally, regarding point 5, please note that ATSDR develops minimal risk levels (MRLs), not reference doses, for non-cancer effects, and ATSDR does not develop cancer slope factors or other toxicity factors for carcinogenic effects.
- p. 4, *Article Inclusion Criteria* section. "Published in 2000 or later (to capture information published after the 2000 Guidance)." A minor comment is that the literature search for the 2000 Guidance likely ended prior to 2000, since it took time for development and review of a document prior to the date when it was finalized. Does the 2000 Guidance include the date when the literature search that was used was performed?
- p. 5, *Keywords.* The literature search strategy (e.g., how AND, OR, etc. were used with the keywords listed) should be provided. Additionally, does "states" mean "state environmental agencies," and how were the states listed selected?

  Were publications by the Delaware River Basin Commission (DRBC) and other similar interstate authorities (e.g., Ohio River Valley Water Sanitation Commission [ORSANCO]) included? DRBC has conducted multiple studies of emerging contaminants in fish, including pharmaceuticals, flame retardants, PFAS, and others. See https://www.nj.gov/drbc/programs/quality/cecs.html
- p. 5, *Weight of evidence analysis.* The weight of evidence approach, based on the information presented here, does not appear to be completely logical and supportable.

  Specifically, one of the four criteria used to assign points is "species found in the U.S." However, the *Overview* section (p. 1) says that articles that contained "fish not found in U.S. waters" were removed. Based on this statement, it appears that all articles that were included contained information on species of fish found in the U.S. However, this is inconsistent with the weight of evidence discussion (p. 5), in which it appears that a paper would be included even if it was not assigned 1 point for "species found in the U.S." if it was assigned 2 points for meeting two other criteria.

Additionally, it is unclear how a study could meet the criterion for including "BCF or BAF data" without also meeting the criterion for including "information on the contaminant's detection in fish." Furthermore, even if a study provided a BCF or BAF for a contaminant without contaminant concentration data, the study would have been removed, since it is stated in first full paragraph of p. 7 that "EPA removed compounds without concentration data…".

Based on the above, it appears that all included studies would have met the following two criteria: including "information on the contaminant's detection," and including information on "species found in the U.S."

Also, the criterion for "oral toxicity data" is unclear. Does this mean data from studies of oral toxicity in mammalian species, or does this mean an oral toxicity factor (e.g., reference dose, cancer slope factor)?

- p. 7, *Researched Toxicity Values* section. The review document does not mention that the process used for selection of the toxicity values in the review document differs from the process used by in the EPA (2015) that is cited, and clarification of this issue needs to be added. Specifically, while the list of eight sources of toxicity values in the review document is the same as the list used by EPA (2015), the process for selection of the toxicity factor in the review document is not the same as in EPA (2015). In the review document, toxicity values were selected from the eight sources listed based on the order in which the source is listed (i.e., when toxicity values were available from multiple sources, the toxicity value from the source highest on the list was used). In contrast, EPA (2015) used a different process to select from among the available toxicity factors. The description of this process is included in each of the contaminant-specific " Update of Human Health Ambient Water Quality Criteria" documents (linked from the table of human health criteria at https://www.epa.gov/wqc/national-recommended-water-quality-criteria-human-health-criteria-table; for example, see https://www.epa.gov/sites/default/files/2015-10/documents/final-1-1-1-trichloroethane.pdf) and is copied below:

  "After identifying and documenting all available toxicity values, EPA followed a systematic process to select the toxicity values used to derive the AWQC for noncarcinogenic and carcinogenic effects. EPA selected IRIS toxicity values to derive the updated AWQC if any of the following conditions were met:

  1. EPA's IRIS toxicological assessment was the only available source of a toxicity value.
  2. EPA's IRIS toxicological assessment was the most current source of a toxicity value.
  3. EPA's IRIS program was reassessing the chemical in question and had published the draft Toxicological Review for public review and comment, discussion at a public meeting, and subsequent expert peer review.
  4. The toxicity value from a more current toxicological assessment from a source

other than EPA IRIS was based on the same principal study and was numerically the same as an older EPA IRIS toxicity value.

5. A more current toxicological assessment from a source other than EPA IRIS was available, but it did not include the relevant toxicity value (chronic-duration oral RfD or CSF).
6. A more current toxicological assessment from a source other than EPA IRIS was available, but it did not introduce new science (e.g., the toxicity value was not based on a newer principal study) or use a more current modeling approach compared to an older EPA IRIS toxicological assessment.

EPA selected the toxicity value from a peer-reviewed, publicly available source other than EPA IRIS to derive the updated AWQC if any of the following conditions were met:

1. The chemical is currently used as a pesticide, and EPA Office of Pesticide Programs had a toxicity value that was used in pesticide registration decision-making.
2. A toxicological assessment from a source other than EPA IRIS was the only available source of a toxicity value.
3. A more current toxicological assessment from a source other than EPA IRIS introduced new science (e.g., the toxicity value was based on a newer principal study) or used a more current modeling approach compared to an older EPA IRIS toxicological assessment."

- p. 7, *Researched Toxicity Values* section. The hotlinks in this section of the review document do not work. It is assumed that this will be fixed in the final version.
- p. 7, *Researched Toxicity Values* section, toxicity values for PFAS. The toxicity values for PFNA and PFHxS referred to as "reference doses" from the proposed EPA (2023) National Primary Drinking Water Regulation (NPDWR) are called "chronic reference values" not "reference doses." The proposed rule states that, for PFNA and PFHxS, "a chronic reference value based on an Agency For Toxic Substances And Disease Registry (ATSDR) intermediate-duration oral Minimal Risk Level" was developed.

  A draft IRIS reference dose for PFHxS is now available, and a draft IRIS reference dose for PFNA will be released soon. Since the draft IRIS PFDA value is used in the review document, it is suggested that the draft IRIS PFHxS value (and the draft IRIS PFNA values, when available), which are more recent than the ATSDR/NPDWR values, also be used. Relevant to this point, a key difference between the recent reference doses for long-chain PFAS developed by EPA (Office of Water – PFOA, PFOS; IRIS – PFDA, PFHxS) and the ATSDR Minimal Risk Levels for long-chain PFAS (PFOA, PFOS, PFNA, PFHxS) is that the EPA toxicity values are based on human data, and they are much more stringent than the ATSDR values based on animal data.
- p. 7, *Screening Level Calculations and Analysis,* general comment. For contaminants with a very low Reference Dose or a high cancer potency (slope factor), general dietary exposure

in the general population may exceed the exposure from consumption of a weekly fish meal at the screening concentration. In such cases, it is not beneficial from a public health viewpoint to issue a fish consumption advisory based on the screening concentration because other foods that do not have the health benefits associated with fish will be consumed instead of fish, while exposure to the contaminant will still be above the toxicity value. This situation is much more likely to occur if fish consumption advisories for carcinogens are based on the 10^{-6} risk level instead of the 10^{-5} risk level, as was done in the screening level calculations in the review document (p. 9).

In such cases, alternative approaches for development of fish consumption advisories may be considered. For example, in New Jersey's development of fish consumption advisories for dioxins and related compounds, the lifetime cancer risk resulting from background dietary exposures to dioxin-like compounds was estimated to be about 10^{-3}. For this reason, an advisory based on 10^{-5} or 10^{-6} risk would not result in a reduction of risk from dioxins and related compounds. Therefore, the advisories were developed using an alternative approach based on comparison with background dietary exposures.

For the general population, it was recommended that the fish consumption advisory be based on an intake of dioxin and related compounds equal to the daily background exposure in the total diet, such that consumption of fish at the advisory level would result in a doubling of the background exposure. The advisory for the high-risk population (pregnant and nursing mothers, women of childbearing age, and young children) considered the fact that consumption of fish is beneficial as part of a healthy diet. For this population, it was recommended that daily dioxin exposure from consumption of fish should not exceed twice the exposure of an average meal, and it was concluded that this exposure was likely to fall within the range of normal dietary variation.

- p. 7, *Screening Level Calculations and Analysis.* It should be clarified in the text (not just in the equation and the footnote) that the screening values for the general population (adult and pregnant individual) developed in the review document are based on weekly consumption of one 8-ounce fish meal. This is important because the EPA (2000) guidance that is cited (Volume 2, Section 3) provides information for developing screening values based on several different consumption frequencies.

- p. 8, last paragraph, "generic" screening level. It is recognized that a "generic" toxicity value for screening of contaminants for which no toxicity value is available is needed. Based on the bioaccumulative potential and low-dose toxicity of long-chain PFAS, it is likely that a toxicity value based on a long-chain PFAS such as PFNA will be protective for most other contaminants. That being said, the "generic" screening level based on a toxicity value of 3×10^{-6} mg/kg/day (based on the ATSDR MRL) for PFNA is highly uncertain.

  Additionally, it is stated that the "lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed)" was used for the generic screening value. However, as discussed above, IRIS is currently developing Reference Doses for

several long-chain PFAS based on human data, and these IRIS Reference Doses are lower than the ATSDR MRLs based on animal data. It is likely that the draft IRIS toxicity assessment for PFDA, which includes a much lower Reference Dose than the ATSDR PFNA value used here, will be finalized soon. When this occurs, will the "generic" toxicity value be revised?

For contaminants that do not have a toxicity value in the eight sources listed in the review document, chemical-specific toxicity values from other sources (e.g., values developed by state environmental or health agencies other than California EPA) could be reviewed and considered. It is stated in the section on *Researched Toxicity Values* that other sources were not used "because of the variability of methods applied and inconsistency of the existence of adequate quality control documentation." However, it is unlikely that chemical-specific values developed by states (e.g., New Jersey, Minnesota, Massachusetts) using EPA risk assessment guidance are more uncertain than a "generic" value based on the toxicity value for a different chemical. As one example, New Jersey has developed a Reference Dose of 1.3 x 10^{-6} mg/kg/day (1.3 ng/kg/day) for perfluoroundecanoic acid specifically for use in fish consumption advisories. See https://dep.nj.gov/wp-content/uploads/dsr/pfunda-fish-consumption-trigger.pdf.

- Comments on screening levels in Excel spreadsheet:
    - In these spreadsheets, the concentration data in columns G, H, and I are shown in units of ng/g (which is ppb, although not stated) but the Screening Levels in the columns to the right are shown in units of µg/g (ppm). This inconsistency in units is confusing and may easily be overlooked by the reader, and consistent units should be used.
    - The Screening Level for lead is based on cancer risk using the CalEPA (2011) cancer slope factor because no Reference Dose is available for lead. The reason that there is no Reference Dose for lead is because there is no known threshold for the neurodevelopmental effects of lead in children, and these neurodevelopmental effects are generally the focus of concern regarding risks of lead exposure. If possible, development of a Screening Level and fish consumption advisory for lead that is protective for neurodevelopmental effects of lead in children, using the EPA Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) model, could be considered. New Jersey has used such an approach for its fish consumption advisories for lead.
    - The cancer slope factor for PFOA of 0.0293 mg/kg/day shown in the "fillet-analysis w tox info" and "shellfish-analysis w tox info" spreadsheets is incorrect. The cancer slope factor from the cited EPA (2023) reference is 0.0293 **ng/kg/day**, which is 29,300 mg/kg/day.
    - The cancer slope factors for PFOA and PFOS are missing from the "WholeBody-analysis w tox info" spreadsheet.

2. Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?

Response: The list of contaminants to monitor for advisories in Table 7 appears reasonable. It should be noted that New Jersey and other states already have developed fish consumption advisories for many of the contaminants in Table 7. Of the chemicals included on this list, New Jersey has developed fish consumption advisory triggers and/or waterbody-specific fish consumption advisories for PFOA, PFOS, PNA, microcystins, and lead. Several other states have also developed fish consumption advisories for PFAS. California has also developed consumption trigger for microcystins, and other states may also have developed advisories for contaminants on this list.

The list of contaminants to monitor to watch in Table 8 also appears to be reasonable.

3. Are there additional contaminants that should be included in the "monitor for advisories" list or "monitor to watch" list? If so, what are they, and why should they be included?

Response: The list of additional contaminants in the "monitor for advisories" and "monitor to watch" lists include the contaminants identified through the process described in the review document.

Inclusion of additional cyanotoxins (e.g., cylindrospermopsin, anatoxin-a, and/or saxitoxin) could be considered since potential risks from fish from waterbodies with harmful algal blooms (HABs) are of current concern. New Jersey and California have developed fish consumption triggers for cylindrospermopsin and anatoxin-a, and other states have developed qualitative advice for consumption of fish where HABs have occurred. Advisories for cyanotoxins should consider the fact that exposure to cyanotoxins in fish is likely to be short-term or subchronic, rather than chronic, due to the relatively short timeframe that a HAB persists in a waterbody.

Requested Clarification from EPA

Questions for Reviewer 2:

1. When calculating a generic screening level for contaminants that do not have a toxicity value in the eight sources listed in the review document or developed by state environmental or health agencies, what do you recommend EPA do?
2. Are you in favor or opposed to the idea of a generic screening level in those cases?
3. If in favor, what reference dose do you recommend EPA use?

Reviewer 2 Responses:

1. I addressed this question in the last paragraph of my comments on the generic screening level (copied below), and EPA should review that part of my comments. In summary, for contaminants that do not have a toxicity value in the eight sources listed in the review document, I recommend that chemical-specific toxicity values from other sources (e.g., values developed by state environmental or health agencies other than California EPA) be reviewed and considered.

2. If no chemical-specific toxicity value that is considered to be acceptable is located, then I agree that use of a generic value is necessary.
3. By its nature, the generic screening level is highly uncertain. The generic value should be selected with the expectation that it will be protective for most or all chemicals without toxicity values. EPA's proposed generic screening value of 3 x 10-6 mg/kg/day, based on the ATSDR MRL for PFNA, is acceptable from a numerical viewpoint. However, the EPA document states that the generic value selected is "the lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed) available among the contaminants found in fish". The final ATSDR MRL for PFOS (2 x 10-6 mg/kg/day) is lower than the ATSDR MRL for PFNA (3 x 10-6 mg/kg/day) which was selected as the generic screening value. As such, it is unclear why the lower PFOS MRL was not selected as the generic screening value.

My earlier comments about the generic screening level are on p. 6 of my response to the charge questions [included again below].

FROM p. 6 OF MY EARLIER RESPONSES TO CHARGE QUESTIONS:

p. 8, last paragraph, “generic” screening level. Itis recognized that a “generic” toxicity value for screening of contaminants for which no toxicity value is available is needed. Based on the bioaccumulative potential and low-dose toxicity of long-chain PFAS, it is likely that a toxicity value based on a long-chain PFAS such as PFNA will be protective for most other contaminants. That being said, the “generic” screening level based on a toxicity value of 3 x 10-6mg/kg/day (based on the ATSDR MRL) for PFNA is highly uncertain.

Additionally, it is stated that the “lowest final toxicity value (that is, the most stringent toxicity value that was not draft or being developed)” was used for the generic screening value. However, as discussed above, IRIS is currently developing Reference Doses for several long-chain PFAS based on human data, and these IRIS Reference Doses are lower than the ATSDR MRLs based on animal data. It is likely that the draft IRIS toxicity assessment for PFDA, which includes a much lower Reference Dose than the ATSDR PFNA value used here, will be finalized soon. When this occurs, will the “generic” toxicity value be revised?

For contaminants that do not have a toxicity value in the eight sources listed in the review document, chemical-specific toxicity values from other sources (e.g., values developed by state environmental or health agencies other than California EPA) could be reviewed and considered. It is stated in the section on Researched Toxicity Values that other sources were not used “because of the variability of methods applied and inconsistency of the existence of adequate quality control documentation.” However, it is unlikely that chemical-specific values developed by states (e.g., New Jersey, Minnesota, Massachusetts) using EPA risk assessment guidance are more uncertain than a “generic” value based on the toxicity value for a different chemical. As one example, New Jersey has developed a Reference Dose of 1.3 x 10-6 mg/kg/day (1.3 ng/kg/day) for perfluoroundecanoic acid specifically for use in fish consumption advisories. See https://dep.nj.gov/wp-content/uploads/dsr/pfunda-fish-consumption-trigger.pdf .

COMMENTS SUBMITTED BY

REVIEWER 3

External Peer Review of the Process for Selecting Contaminants to Monitor in Fish Advisory Programs

Charge Questions

1. Is the process EPA followed to identify compounds for which fish and shellfish advisories might be needed reasonable?

Yes, overall, the process EPA followed to identify priority compounds is reasonable. However, EPA might consider revising the documentation and analyte selection process in these areas:

1. Update the equations used to calculate screening levels (SLs) to more closely align with current fish advisory practices. The current equation cites to the 2000 guidance, which is a special case of a more general equation.
2. Provide more analysis and documentation of the fish tissue concentrations summarized from the literature, particular for analytes that are selected because the sample maximum concentrations exceeds the SL.
3. Consider providing different weighting factors to these two conditions:
   A. sample maximum > SL and sample mean ≤ SL
   B. sample maximum > SL and sample mean > SL
4. Consider refining the decision process for selecting an RfD to serve as a protective surrogate value when the RfD is missing for a chemical.
5. Derive a SL for lead (Pb) using EPA's lead risk models, rather than the cancer slope factor.
6. Either exclude the lipid-normalized concentrations, or apply a default assumption for lipid content to convert the values to wet weight units.

The basis for each recommendation is provided below.

Screening Level (SL) Equations

Separate equations for calculating a fish tissue screening level (SL) are provided for noncancer and cancer endpoints. The equations are consistent with the 2000 Guidance, but could be updated to more clearly show the underlying assumptions and to reflect how states currently implement fish advisories. Applying abbreviations for convenience, the equation presented to calculate a screening level for noncancer effects (SL_{nc}) on p.7, including the unit conversion factor (CF) for mass discussed on p. 8, is:

$$SL_{nc} = \frac{RfD \times BW}{CR \times CF} [=] \frac{\text{(mg COPC/kg BW-day)} \times \text{(kg BW)}}{\text{(g ww/day)} \times 0.001 \text{ kg/g}}$$

where,

SLnc = fish tissue concentration (mg/kg ww)

RfD = chronic oral refence dose (mg/kg-day)

BW = body weight (kg)

CR = average daily fish consumption rate (g ww/day)

CF = conversion factor (0.001 kg per g)

What is implied, but not stated directly, is that the SL is the concentration that, when included in the calculation of average daily dose (ADD), equals the RfD. In other words, the ratio of the ADD/RfD is 1, or equivalently, the target hazard quotient (THQ) is 1. Also, in practice, most state agencies consider fish consumption rate to be the product of the meal size and meal frequency, which is how different meal frequencies are ultimately determined. Finally, some agencies also apply a relative source contribution (RSC) to account for additional exposure pathways that may contribute to a total average daily dose. Considering all of these concepts, a more general expression for SL is:

$$SL_{nc} = \frac{THQ \times RfD \times RSC \times BW}{(MS \times MF) \times CF}$$

where,

SLnc = fish tissue concentration (mg/kg ww)

THQ = target hazard quotient

RfD = chronic oral refence dose (mg/kg-day)

RSC = relative source contribution

BW = body weight (kg)

MS = meal size (g ww/meal)

MF = average daily meal frequency (meals/day)

CF = conversion factor (0.001 kg per g)

Then, it can be stated that two assumptions used in the SL are: 1) THQ =1 (which would open the door for some discussion on the science policy decision, and standard conventions used by USEPA in selecting a target level); and 2) RSC = 1 (which would also open the door for some discussion on why this is used in the SL derivation, but might be revisited in site-specific applications).

The product of (MS x MF) is CR, and USEPA can continue to present the CR estimates for typical and high-end consumers, and briefly discuss what meal frequency these correspond to when expressed over a period of one month or one year.

A similar general equation can be presented for the SL for cancer endpoints.

Summary of Occurrence Data on Concentrations in Fish Tissue

The guidance document discuss the literature review methods and data usability criterion. The occurrence data generated from this process are provided in the Excel file (Screen Level Calculations.xlsx), grouped into separate worksheets for: 1) fillet data; 2) whole body data; 3) shellfish data. The occurrence data are distilled down to two summary statistics – “Maximum” and “Average”.

The sample maximum is a very unstable summary statistic, and subject to extreme results that do not actually represent the conditions found in most water bodies in the United States. The

chances of observing an extreme value actually increases with increasing sample sizes. It is clear that one of the reasons for selecting the maximum is that the choice of statistics is limited to a large extent by the information presented in table summaries in the literature – it is unreasonable to expect to obtain the underlying raw data from most published studies. However, a preferred (more stable) statistic, that achieves the goal of representing a high-end value, would simply be an upper percentile (e.g., 95th percentile, or even 99th percentile). A recommended hierarchy of summary statistics for representing a high-end value is:

- Reported upper percentile (90th, 95th, or 99th)
- Estimate of upper percentile based on an assumed distribution (e.g., mean and standard deviation are reported, so assume a lognormal distribution to estimate the corresponding 95th percentile)
- Sample maximum

The following extreme cases of sample maximums are noted by comparing the ratio of the sample maximum to the arithmetic mean:

Worksheet	Chemical	Maximum (ng/g)	Average (ng/g)	Ratio of Max/Average
Fillet	PFDoA	859,000	4.2	204,135
Fillet	PFOS	2,840,000	53.1	53,525
Whole Body	BDE-99	650	0.24	2,708

Given the unreliability of the sample maximum as an indicator of conditions on a national scale, the rather large set of analytes for which only a maximum is provided (there are no estimates of the mean) should be carefully considered, at least in terms of the weighting scores used to rank each analyte. The following counts of analytes for which no "average" is available are noted, by chemical class:

Worksheet	Chemical Class	Number of Analytes Missing an Average
Fillet	Flame Retardants	16
	PFAS	12
	Metals	1
	Chlorinated	1
	Cyanotoxin	1
	Other (paraffins)	2
Whole Body	Flame Retardants	8
	PFAS	3

	Metals	1
	Other (paraffins)	1

The one metal listed in the table above is for lead. Lead is included in this guidance based on the cancer slope factor, which is an extremely unusual choice. From my experience as a toxicologist and frequent participant on EPA's science advisory panels involving lead, lead is not regulated based on the cancer slope factor at any site, for any medium. USEPA and state agencies rely instead on the screening levels developed from regulatory models that predict blood lead concentrations (e.g., IEUBK or Adult Lead Model) from average daily intake. The USEPA Regional Screening Level tool[1] and guidance notes, "EPA has no consensus RfD or SFO for inorganic lead, so it is not possible to calculate SLs as we have done for other chemicals". EPA should develop a generic fish tissue level using one of EPA's lead models. For example, alternative dietary inputs can easily be included in the IEUBK model for children to develop a protective SL for lead in fish tissue.

Consider also including the number of studies and the number of study values that were curated from the literature and used to derive the "Maximum" and "Average".

Do not include the tissue concentrations that are lipid normalized, directly in the comparison to the toxicity values. The units matter in this case. A preferred approach would be to apply a general assumption for % lipid content to convert the lipid-normalized values to wet weight concentrations. Or, alternatively, exclude the study results that are expressed only as lipid normalized values.

Surrogates RfD for Missing Values

EPA elected to the RfD for PFNA (3E-06 mg/kg-day) as the proxy value for analytes without an RfD because, "it is the lowest final RfD for all contaminants being considered for inclusion in the monitoring list". In the Excel file, these are listed as "generic SLs" and include chemicals from a wide range of categories: antibacterials and antibiotics, cyanotoxins, flame retardants, and pharmaceuticals. This extrapolation across chemical classes seems unnecessary when it is possible to select from the lowest RfD with the same chemical class.

2. Is the list of contaminants advisory programs should consider monitoring for reasonable (e.g., reflects the current range of contaminants detected in fish with potential human health impacts)?

Yes, the range of chemical classes makes sense and appears to be comprehensive. See above for recommendations on revisiting the approach used to derive SLs for some of these analytes.

3. Are there additional contaminants that should be included in the "monitor for advisories" list or "monitor to watch" list? If so, what are they, and why should they be included?

I am not aware of any additional contaminants that would be reasonable candidates to include in the monitoring lists.

[1] https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search

Requested Clarification from EPA

Question for Reviewer 3:

When calculating a generic screening level, you recommended selecting the lowest RfD from the same chemical class. If a chemical class does not have a contaminant with a final reference dose (e.g., paraffins), what would you recommend that EPA do?

Reviewer 3 Response:

For chemicals that are part of a chemical class that does not have a final toxicity value (reference dose or oral cancer slope factor), there are 3 options that can be pursued:

1. Apply toxicity values developed by another program office of USEPA
2. Use established computational toxicity models to identify a suitable surrogate chemical/chemical class from which to estimate the toxicity value. There is an extensive effort within EPA to develop tools and frameworks for just this purpose.
3. Do not develop a fish advisory at this time. The rationale would be that Approaches 1 and 2 introduce too much uncertainty to develop a risk-based fish tissue concentration.

In the case of paraffins (polychlorinated n-alkanes), EPA has published several reviews of the literature on animal toxicity and human epidemiological data. The most recent was prepared by EPA/OPPT for the TSCA Section 5 New Chemicals Program. The December 22, 2015 report is available online here:

https://www.epa.gov/sites/default/files/2015-12/documents/dover_-_standard_review_risk_assessment_p-12-0282-0284_docket_0.pdf

- Section 4 (Human Health Hazard Overview) summarizes the literature on medium-chain chlorinated paraffins (MCCP) and long-chain chlorinated paraffins (LCCP).
- Tables 9 and 10 present dose estimates from drinking water and fish consumption based on modeled exposure concentrations.
- Sections 6.1.2 and 6.2.2 present the exposure and risk evaluations relevant to oral exposure via fish consumption, and how toxicity values were derived from selected points of departure (PODs) derived from key animal toxicity studies.

While the use of these toxicity values, with attribution to EPA/OPPT, introduces some uncertainty in the fish advisory calculations, there is less uncertainty applying these values than using PFNA as a surrogate for all chemicals.