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HEALTH ADVISORY FOR PERFLUOROHEXANOIC ACID (PFHxA) CHEMICAL ABSTRACT SERVICES REGISTRY NUMBER (CASRN) 307-24-4

Prepared by:
Office of Toxicity Assessment
Illinois Environmental Protection Agency
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REASON FOR ACTION

As a result of a Per- and Polyfluoroalkyl Substances (PFAS) sampling initiative of community water supplies (CWS) undertaken by the Illinois Environmental Protection Agency (Illinois EPA), Perfluorohexanoic Acid (PFHxA) has been confirmed in a well at a CWS. In accordance with 35 Illinois Administrative Code 620.605(a), the Illinois EPA is issuing a health advisory for Perfluorohexanoic Acid. Section 620.605(a) directs the Illinois EPA to issue a health advisory for a chemical substance if all of the following conditions are met:

- 1) A community water supply well is sampled, and a substance is detected and confirmed by resampling;
- 2) There is no standard under Section 620.410 for such chemical substance; and
- 3) The chemical substance is toxic or harmful to human health according to the procedures of Appendix A, B, or C.

The health advisory guidance level for PFHxA is 0.56 milligrams per liter (mg/L), or 560,000 nanograms per liter (ng/L) or parts per trillion (ppt).

The health advisory will be published in the Environmental Register (publication of the Illinois Pollution Control Board) and placed at the website: <https://pcb.illinois.gov/Resources/News>

The health advisory will also be placed on Illinois EPA's website at:
<https://www2.illinois.gov/epa/topics/water-quality/pfas/Pages/pfas-healthadvisory.aspx>

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PURPOSE OF A HEALTH ADVISORY

In accordance with 35 Ill. Adm. Code 620.601, the purpose a health advisory is to provide guidance levels that, in the absence of an applicable groundwater quality standard under Section 620.410, and must be considered by Illinois EPA in: 1) establishing groundwater cleanup or action levels whenever there is a release or substantial threat of a release of a hazardous substance, pesticide, or another contaminant that represents a significant hazard to public health or the environment; 2) determining whether a community water supply is taking its raw water from a site or source consistent with regulatory requirements; and 3) developing Illinois Pollution Control Board (Board) rulemaking proposals for new or revised numerical standards.

Health advisories serve as informal technical guidance, intended to provide information about contaminant exposures and potential public health impacts. The guidance levels represent concentrations in drinking water at which no adverse health effects are expected to occur. Guidance levels are not enforceable or intended to be used as drinking water standards, also known as maximum contaminant levels (MCLs).

HEALTH ADVISORY GUIDANCE LEVEL FOR PFHxA

Through issuance of this Health Advisory, Illinois EPA is providing public notice of its guidance level for PFHxA in drinking water. For non-carcinogenic health effects, the guidance level is 0.56 milligrams per liter (mg/L), or 560,000 nanograms per liter (ng/L) or parts per trillion (ppt).

Section 620.605 prescribes the methods for developing health advisories for carcinogens and non-carcinogens. PFHxA does not meet the definition of a “carcinogen”, as defined in Section 620.110; therefore, the method for developing a health advisory for non-carcinogens was used. Briefly, this method specifies that the United States Environmental Protection Agency (U.S. EPA) MCL or maximum contaminant level goal (MCLG) is the guidance level, if available, or the human threshold toxicant advisory concentration (HTTAC) must be determined using the procedures contained in Appendix A of Section 620. U.S. EPA has not published an MCL or MCLG for PFHxA; therefore, Illinois EPA used the Appendix A procedures to calculate a HTTAC for PFHxA.

Appendix A specifies, in prescribed order, the toxicological data to be used in developing guidance levels. To determine appropriate toxicological data in accordance with nationally accepted guidelines, pursuant to the Illinois Groundwater Protection Act (415 ILCS 55-8(a)), Illinois EPA relied upon U.S. EPA guidance titled, “*Tier 3 Toxicity Value White Paper*” (paper), dated May 16, 2013, prepared by the U.S. EPA Office of Solid Waste and Emergency Response (OSWER) Human Health Regional Risk Assessors Forum. The paper lists a hierarchy of sources to be used when determining an appropriate toxicological value for use in human health assessments. The hierarchy for selection of toxicity values is as follows:

Tier 1: U.S. EPA Integrated Risk Information System (IRIS).

Tier 2: U.S. EPA Provisional Peer-Reviewed Toxicity Values (PPRTVs).

Tier 3: In the order in which they are presented:

- 1) The U.S. Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR) Dose Minimal Risk Levels (dose MRLs).
- 2) California EPA, Office of Environmental Health Hazard Assessment (OEHHA).
- 3) PPRTV “Appendix” Values.
- 4) Health Effects Assessment Summary Table (HEAST).

The paper also references peer-reviewed toxicity values developed by other states to calculate provisional drinking water health advisory levels as a Tier 3 source, however, the source is not ranked.

No toxicity values are available from the named sources within the tier. In 2019, the State of Michigan Science Advisory Workgroup issued a document, titled, “*Health-Based Drinking Water Value Recommendations for PFAS in Michigan*”. The document recommended a chronic oral reference dose (RfD) equal to 0.083 milligrams per kilogram per day (mg/kg-day). The RfD is based on a study by Klaunig, et al., titled, “*Evaluation of chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats*”, published in 2015. The study lists critical effects as renal tubular degeneration and renal papillary necrosis of the kidney. In 2019, Luz, et al., published a paper titled, “*Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment*”, which evaluated several studies for the development of a PFHxA toxicity value. Luz, et al., utilized a benchmark dose model for calculating a human equivalency dose (HED) of 24.8 mg/kg-day as the point of departure (HED POD). In 2020, Michigan adopted an enforceable drinking water standard in the form of an MCL for PFHxA, based on the above-referenced studies.

A total uncertainty factor (UF) of 300 (a UF of 10 to account for intrahuman variability, UF of 3 to account for toxicodynamic differences between animals and humans, UF of 10 to account for database uncertainties, including the lack of additional chronic toxicity studies, no additional data in a second species, and concern for decreased vaccine response, and UF of 1 to account for extrapolating from a lowest observed adverse effects level (LOAEL) to a no observed adverse effect level (NOAEL)) was applied to the HED POD.

$$RfD = \frac{HED\ POD}{UF}$$

$$RfD = \frac{24.8\ mg/kg\text{-}day}{300}$$

$$RfD = 0.083\ mg/kg\text{-}day$$

Rounded to one significant digit:

$$RfD = 0.08 \text{ mg/kg-day}$$

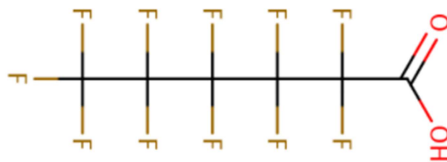
Using the RfD of 0.08 (8E-02) mg/kg-day, and the procedures outlined in Section 620. Appendix A, the recommended guidance level for drinking water is 0.56 milligrams per liter (mg/L), or 560,000 nanograms per liter (ng/L) or parts per trillion (ppt).

CHEMICAL CHARACTERISTICS AND POTENTIAL ADVERSE HEALTH EFFECTS

General Description of PFHxA

Perfluorohexanoic Acid (PFHxA) (CASRN 307-24-4), also known as undecafluorohexanoic acid or PFHxA, is a synthetic chemical which is part of a larger class of chemicals referred to as per- and polyfluoroalkyl substances. PFAS have been manufactured since the middle 20th Century and are known for their chemical and physical properties that impart oil and water repellency, temperature resistance, and friction reduction to a wide range of products, including, but not limited to, textile coatings, paper products, food wrappers, cosmetic and personal care products, non-stick cookware and fire-fighting foams. PFAS are also used in the semiconductor, aerospace, oil production, mining, and metal plating industries, to name a few. PFAS enter the environment through industrial manufacturing and the use and disposal of PFAS-containing products. The chemical and physical properties of PFHxA make it mobile, persistent and bioaccumulative, meaning fish and other animals may accumulate PFHxA in animal tissue when their food sources are contaminated with PFHxA. PFHxA is known to be persistent in the environment.

Structural Identifier



Chemical Identifier



Potential Adverse Health Effects of PFHxA

Studies for human health effects for PFHxA are lacking. Information regarding health effects of PFHxA are derived from animal studies, primarily via the ingestion, or oral exposure, route. Laboratory studies observed the following effects in animals exposed to PFHxA:

- Cellular effects in kidneys
- Decreased weight of offspring
- Increased triglycerides
- Reduced red blood cell count

Carcinogenic Potential

Section 620.110. defines a carcinogen as a contaminant that is classified as: 1) a Category A1 or A2 Carcinogen by the American Conference of Governmental Industrial Hygienists (ACGIH); 2) a Category 1 or 2A/2B Carcinogen by the World Health Organization's International Agency for Research on Cancer (IARC); 3) a "Human Carcinogen" or "Anticipated Human Carcinogen" by the United States Department of Health and Human Service National Toxicological Program (NTP); or 4) a Category A or B1/B2 Carcinogen by the U.S. EPA in IRIS or a Final Rule issued in a Federal Register notice by the USEPA. PFHxA is not classified as a carcinogen by any of the above sources.

**ATTACHMENT TO HEALTH ADVISORY
FOR
PERFLUOROHEXANOIC ACID (PFHxA)
CASRN 307-24-4**

OVERVIEW OF KEY STUDIES

For information regarding the studies used for the derivation of Michigan's RfD for PFHxA, refer to the following documents:

“Evaluation of chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats”, available at:

<https://journals.sagepub.com/doi/full/10.1177/0192623314530532>

“Health-Based Drinking Water Value Recommendations for PFAS in Michigan”, available at:

https://www.michigan.gov/documents/pfasresponse/Health-Based_Drinking_Water_Value_Recommendations_for_PFAS_in_Michigan_Report_659258_7.pdf

“Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment”, available at:

<https://www.sciencedirect.com/science/article/pii/S0273230019300194>

DERIVATION OF THE HEALTH ADVISORY FOR PFHxA

The first step in the derivation of a health advisory is to determine whether the chemical substance presents a carcinogenic risk to humans. PFHxA does not meet the definition of a carcinogen as specified in Section 620.110. Therefore, the guidance level will be based on non-carcinogenic effects of this chemical.

In deriving a guidance level to protect against a health effect for which there is a threshold dose below which no damage occurs (i.e., non-carcinogen effects), Section 620.605 specifies that U.S. EPA's MCLG, if available, is the guidance level. U.S. EPA has not published a MCLG for PFHxA; therefore, Illinois EPA must calculate the HTTAC as the guidance level, using the procedures specified in Appendix A of Section 620.

Appendix A specifies in subsection (a) that the HTTAC is calculated as follows:

$$HTTAC = \frac{RSC \cdot ADE}{W}$$

Where:

HTTAC = Human threshold toxicant advisory concentration in milligrams per liter

(mg/L).

RSC = Relative source contribution, the relative contribution of the amount of exposure to a chemical via ingestion of drinking water when compared to total exposure to that chemical from all sources. Valid chemical-specific data shall be used if available. If valid chemical-specific data are not available, a value of 20% (= 0.20) must be used.

ADE = Acceptable daily exposure of a chemical in milligrams per day (mg/d) as determined in accordance with Appendix A, subsection (b).

W = Per capita daily water consumption equal to 2 liters per day (L/d).

Subsection (b) of Appendix A specifies that the ADE be calculated using, in specified order: a U.S. EPA verified RfD (an estimate of a daily exposure to a chemical which is expected to be without adverse health effects for humans for a lifetime of exposure in units of mg/kg-day); a NOAEL which has been identified as a result of human exposures; a LOAEL which has been identified as a result of human exposures; a NOAEL which has been determined from studies with laboratory animals; and a LOAEL which has been determined from studies with laboratory animals.

Illinois EPA selected an RfD of 0.08 (8E-02) mg/kg-day, as the verified RfD for use in calculating the ADE. The ADE equals the product of multiplying the toxicity value by 70 kilograms (kg), which is the assumed average body weight of an adult human per Section 620:

$$ADE = 0.08 \text{ mg/kg-day} \cdot 70 \text{ kg} = 5.6 \text{ mg/day}$$

The next step in the development of the HTTAC is the evaluation of chemical-specific RSC data available for the chemical. Illinois EPA evaluated data from ATSDR, U.S. EPA Office of Water, and values developed by other states. There is little scientific consensus regarding the contribution of drinking water to the total amount of PFAS exposure to humans. Humans are exposed to PFHxA through a variety of media, including, but not limited to air emissions, ingestion of fish or other animals exposed to PFHxA, dermal exposure and incidental exposure from PFHxA-containing consumer products, much of which varies on a site-specific basis. Due to this lack of consensus, Illinois EPA elected to use the conservative default value of 20% (0.20) for its HTTAC calculation.

Finally, the HTTAC is calculated by the product of the RSC and the ADE, divided by the per capita daily water ingestion rate, specified in Appendix A as equal to 2 L/day:

$$HTTAC \text{ (mg/L)} = \frac{0.20 \cdot 5.6 \text{ mg/day}}{2 \text{ L/day}}$$

$$HTTAC \text{ (mg/L)} = \frac{1.12 \text{ mg/day}}{2 \text{ L/day}}$$

$$HTTAC = 0.56 \text{ mg/L}$$

or:

$$560,000 \text{ ng/L or ppt}$$

The final step in ensuring a calculated guidance level is appropriate is to compare the guidance level to the chemical's practical quantitation limit (PQL), or minimum reporting level (MRL). U.S. EPA's Method 537.1 for analyses of PFAS drinking water samples states the PFHxA MRL is 2 ng/L, which is below the calculated guidance level of 560,000 ng/L. Therefore, the guidance level is appropriate.

REFERENCES

- IGA (Illinois General Assembly). Illinois Groundwater Protection Act (IGPA). 415 ILCS 55. Available at: <https://www.ilga.gov/legislation/ilcs/ilcs3.asp?ActID=1595&ChapterID=36>
- Klaunig JE, Shinohara M, Iwai H, et al. 2015. Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. *Toxicol Pathol.* 43(2):209-220.
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- U.S. EPA (United State Environmental Protection Agency) Office of Solid Waste and Emergency Response (OSWER). 2013. Tier 3 Toxicity Value White Paper. OSWER Document Number 9285.7-86. Available at: <https://www.epa.gov/sites/production/files/2015-11/documents/tier3-toxicityvalue-whitepaper.pdf>