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VIRGINIA DEPARTMENT OF HEALTH GUIDELINE FOR ISSUANCE OF FISH CONSUMPTION ADVISORY DUE TO CONTAMINATION OF FISH WITH PERFLUOROOCTANE SULFONATE

Perfluorooctane sulfonate (PFOS) is a synthetic surfactant with unique properties and one of the most studied per- and poly- fluoroalkyl substances (PFAS), which number in the thousands. PFOS is widely used by many industries and for firefighting. PFOS can enter the environment through production or waste streams and is very persistent in the environment. Health studies show that PFOS is prevalent in the population and takes years to be eliminated from the body. PFOS adverse health effects include decreased birthweight, increased cholesterol levels, pregnancy-induced hypertension, and lowered antibody response to certain vaccines. PFOS is of particular concern because it can accumulate up the food chain in aquatic systems and can lead to high concentrations in predatory fish consumed by anglers. This guideline will become effective on October 1, 2024.

Characteristics of Perfluorooctane Sulfonate

Per- and poly- fluoroalkyl substances (PFAS) are synthetic compounds that number in the thousands and are widely used for their chemical and physical properties to repel water and oil, and to resist thermal degradation. While several hundred are reported to be actively used, PFOS is one of the most widely used and studied PFAS. PFOS can be described as having a hydrophobic/lipophobic fluoroalkyl "tail" and polar hydrophilic sulfonate "head." This combination makes PFOS very useful as a surfactant and surface protectant. The strength of the carbon-fluorine bonds makes PFOS very stable in the environment and resistant to biodegradation, photooxidation, direct photolysis, and hydrolysis. The sulfonate functional group of PFOS is negatively charged at environmental pH and influences its mobility in groundwater.

Production and Use of Perfluorooctane Sulfonate Production

PFOS manufacturing began in the United States in 1948. U.S. production volumes of PFOS reported under the U.S. Environmental Protection Agency (EPA) Inventory Update Rule is 10,000 – 500,000 pounds in 1994 and 2002. Electrochemical fluorination was used predominantly in the production of PFOS by its major manufacturer. During electrochemical fluorination octane sulfonyl fluoride ($C_8H_{17}SO_2F$) undergoes electrolysis in anhydrous HF, resulting in all hydrogen atoms being replaced by fluorine atoms. Rearrangement and breakage can occur during the process resulting in branched and linear perfluorinated compounds. In early 2000, the major manufacturer of PFOS voluntarily phased out production of PFOS; however, PFOS is still manufactured in China. PFOS is used in fire-fighting foams, alkaline cleaners, floor polishes, etching acids for circuit boards, metal

plating, and protective coatings for food packaging, carpets, and fabrics. Historical disposal of PFAS-containing waste included landfills, incineration, and sludge.

Sources of Perfluorooctane Sulfonate in the Environment

PFOS is released into the air, water and soil during the manufacturing process. PFOS has been detected in surface water and sediment downstream of production facilities and in wastewater treatment plant effluent, sewage sludge, landfill leachate, and disposal sites. Another major source of PFOS in the environment is where PFOS firefighting foam is stored or used during firefighting training exercises or at airplane crash sites. Because of its persistence, it can be transported long distances in air or water. This is evident in PFOS detections in Arctic media and biota, including polar bears and fish found in remote areas. Historically, land application of biosolids and some aqueous fire-fighting foam used during aviation fires and training has been a source of PFOS in surface water and groundwater.

Toxicity of Perfluorooctane Sulfonate

PFOS has been evaluated in a large number of human and laboratory animal studies. The mechanism of toxicity of PFAS has not been fully elucidated. Adverse effects in laboratory animals involve the activation of peroxisome proliferator-activated receptor-α (PPARα). This receptor can mediate many biological responses. Humans are less responsive to PPARα agonist, and this may explain the toxicity differences between species. Generally, epidemiological studies use serum PFAS levels as biomarkers of exposure, whereas animal studies use daily doses. Comparison of the toxicity of PFAS in general across species is difficult due to differences in elimination half-lives, lack of adequate mechanistic data, species differences in the mechanism of toxicity for some endpoints, and differences in measurement of exposure levels between epidemiological and experimental studies. Epidemiology studies provide important data to establish links between PFOS and human health effects. PFOS effects on liver enzymes, birth weight, and antibody response in laboratory animals are supported by epidemiology studies. Uncertainties with human data make animal studies better for assessing PFOS effects quantitatively.

The primary route of exposure to PFOS is ingestion. Contaminated drinking water is the primary source of exposure for the general population. Communities where PFOS has been released into the environment may result in PFOS bioaccumulating in fish. In humans, PFOS is distributed mostly to the liver and blood and binds non-covalently to plasma proteins. Binding to albumin causes a conformational change thereby affecting its affinity for endogenous compounds also transported by serum albumin. PFOS does not go under any metabolism and is excreted from the body primarily in urine and feces unchanged. Urinary excretion of PFOS is affected by the presence of other PFAS in the blood and the age and gender of the individual. After exposure to PFOS, it remains in the body for many years. The arithmetic mean serum elimination half-life of PFOS reported for retired fluorochemical workers is 5.4 years. Serum levels PFOS in the general population of the United States have sharply declined in recent years. The National Health and Nutrition Examination Survey reported PFOS serum concentration of 30.4 nanogram/milliliter (ng/mL) in 1999-2000. This is in contrast to 2018 data where the general population PFOS serum concentration was reported as 4.25 ng/mL, representing over an 85% decline.

Human PFOS studies come largely from the C8 Science Panel research of 69,000 participants from communities in Ohio and West Virginia impacted by perfluorooctanoic acid (PFOA) discharge from the DuPont Washington plant in Parkersburg, WV. The study was designed to examine PFOA

health impacts, but the serum samples analyzed also included PFOS. Occupational studies of workers at 3M Decatur, Alabama, and Antwerp, Belgium evaluated PFOS levels and clinical chemistry, hormonal parameters, and hematology. These and other occupational and population studies have been used to evaluate the association between PFOS and health. Health outcomes assessed include blood lipid, thyroid effects, immune function, reproductive effects, pregnancy-related outcomes, fetal growth and developmental outcomes, and cancer. Epidemiological studies suggest associations between PFOS and several health outcomes: pregnancy-induced hypertension, increase in serum hepatic enzymes, increase in serum lipids, decrease in antibody response to vaccines, and decrease in birth weight. There is suggestive evidence of PFOS causing cancer in humans. An increase in testicular and kidney cancer has been reported in PFAS workers exposed to high concentrations.

Animal studies effects observed in rodents exposed to PFAS primarily include liver, immune, and developmental toxicity. Adverse effects in animal studies are associated with doses that resulted in blood or serum levels that were significantly higher than those reported in the general population for perfluoroalkyl workers.

Derivation of Acceptable Concentration of Perfluorooctane Sulfonate in Fish

The formula for calculating an acceptable concentration, corresponding to a recommended two meals per month of PFOS in edible fish tissue, for protecting fish consumers from non-cancer health effects is as follows:

$$C = \frac{RfD \times BW \times T}{MS \times NM}$$

Where:

C = acceptable concentration of PFOS in edible portions of fish in milligrams per kilograms (mg/kg).

RfD = reference dose for PFOS, 1.8×10^{-6} mg/kg-day.

BW = consumer adult body weight in kilograms (80 kg).

T = time period, (30 days/month).

MS = average fish meal size, 8 ounces (oz) or 0.227 kg.

NM = number of allowable meals per month (2 meals/month).

Substituting these into the above equation, an acceptable PFOS concentration of 0.01 mg/kg or 0.01 parts per million (ppm) in edible fish tissue was calculated:

$$C = \frac{1.8 \times 10^{-6}\ \text{mg/kg-day} \times 80\ \text{kg} \times 30\ \text{days/month}}{0.227\ \text{kg/meal} \times 2\ \text{meals/month}}$$

$$C = 0.0095\ \text{mg/kg} \approx 0.01\ \text{mg/kg} = 0.01\ \text{ppm}$$

The variables used in deriving the acceptable concentration are described as follows:

Concentration (C)

Acceptable concentration of PFOS (mg/kg) in edible portions of fish tissue.

Reference Dose (RfD)

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data.
VDH reviewed PFOS animal and human toxicity peer reviewed studies and reference doses developed by U.S. Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), and several state agencies including California Environmental Protection Agency (CalEPA), and New Jersey's Drinking Water Quality Institute (DWQI).
The PFOS reference dose (1.8×10^{-6} mg/kg-day) developed by both CalEPA and DWQI was determined to be appropriate for developing a PFOS fish consumption advisory. The critical study used by both agencies was an animal immunotoxicity study by Dong et al. In the study mice were administered PFOS orally for 60 days. The study toxic endpoints identified included a decrease in body, spleen, thymus, and kidney weights, and increase in liver weight. Other significant toxicity endpoints included altered natural killer cell activity, lymphocyte proliferation, and decreased sheep red blood cell-specific IgM plaque forming cell response.

A NOAEL of 0.008 mg/kg-day was identified for decreased plaque forming cell response. Measured PFOS serum concentration in animals administered this dose was 0.674 mg/L.
The serum concentration was used as the point of departure (POD). The POD is the dose-response point that marks the beginning of a low-dose extrapolation. Next, uncertainty factors (UFs) are applied to the serum POD to develop a target human serum concentration (HSC). UFs are 10-fold, default factors used in deriving the RfD from experimental data. A 10-fold factor may be used when necessary to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from sub chronic to chronic exposure); (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) uncertainty associated with extrapolation when the database is incomplete.

Both CalEPA and DWQI applied a total UF = 30 (10×3). Ten for intraspecies variability to account for potentially sensitive humans in the population. Three applied to address differences between humans and animals. The full default UF of 10 can be divided into both toxicokinetic $\sqrt{10} \approx 3$ and toxicodynamic $\sqrt{10} \approx 3$. This is because individual UFs represent log-units and the product of two UFs of 3 is taken to be 10. The toxicokinetic difference between rodent and humans is accounted for by using the measured serum thereby eliminating the toxicokinetic uncertainty and the use of the full interspecies UF of 10.

The target human serum concentration (HSC) is calculated as follows:

$$\text{HSC} = \frac{\text{POD}}{\text{UF}} = \frac{0.674\ \text{mg/L}}{30} = 0.022\ \text{mg/L}$$

The target HSC is multiplied by the daily chemical specific clearance factor (CL) 8.1 x 10^{-5} L/kg-day developed by the U.S. EPA to get the RfD.

$$RfD = HSC \times CL = 0.022\ mg/L \times 0.000081\ L/kg\text{-}day = 0.0000018\ mg/kg\text{-}day$$

This daily dose (1.8×10^{-6} mg/kg-day) will be used as the RfD.

Body Weight (BW)

The average adult body weight is widely accepted by many regulatory agencies for risk assessment and establishing guidelines and standards for chemical exposure. The current average adult body weight is 80 kg.

Time (T)

Time period (30 day/month) was used to calculate fish meal consumption limits in a 30-day period.

Meal Size (MS)

Meal size is defined as the amount of fish (in kilograms) consumed at one meal. An 8-oz (0.227 kg) meal size is used.

Number of Meals (NM)

Number of meals (2 meals/month) consumption limit is expressed as the maximum allowable fish meals in a 30-day time period.

Conclusion

Based on the above calculation, VDH will use 0.01 mg/kg or 10 parts per billion (ppb) of PFOS in fish tissue as the trigger level for the issuance of a fish consumption advisory. VDH will use a three-tiered approach when issuing a fish consumption advisory.

- Average fish tissue PFOS concentrations ranging from non-detectable to below 10 ppb will not warrant issuance of a fish consumption advisory.

- When the average PFOS concentrations in fish range from 10 ppb to 20 ppb, VDH recommends limiting consumption of contaminated species to two meals per month.

- When the average PFOS concentration in fish is greater than 20 ppb, VDH recommends that contaminated fish should not be consumed.

VDH also recommends that pregnant women, nursing mothers, and young children should not consume fish from waterways with a PFOS fish consumption advisory.

References

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