SUMMARY of DRAFT INTERIM SPECIFIC GROUND WATER CRITERION for PERFLUORONONANOIC ACID (PFNA, C9)

(CAS #: 375-95-1; Chemical Structure: $CF_3(CF_2)_7COOH$)

Author: **Gloria B. Post, Ph.D., DABT; NJDEP Office of Science**

Primary Reviewers: **Alan H. Stern, Dr.P.H., DABT; NJDEP Office of Science**
Brian F. Pachkowski, Ph.D.; NJDEP Office of Science

Additional Reviewers: **Jerald A. Fagliano, M.P.H., Ph.D.; NJDOH Environmental & Occupational Health Surveillance Program**
Jessie A. Gleason, M.S.P.H; NJDOH Environmental & Occupational Health Surveillance Program

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Summary

A draft interim specific groundwater criterion for perfluorononanoic acid (PFNA, C9) was developed based on chronic (lifetime) drinking water exposure. The criterion is based on modeling of PFNA levels in blood serum that caused increased maternal liver weight from 16 days of exposure in a mouse developmental study and is further supported by data on effects in the offspring in the same study and on other effects in studies from other laboratories. Appropriate uncertainty factors were applied to account for extrapolation from animals to humans, to protect sensitive human subpopulations, and to account for chronic exposure and gaps in the toxicology database. An estimated blood serum:drinking water ratio of 200:1 in humans from ongoing drinking water exposure was used to develop a water concentration protective of chronic drinking water exposure of 17 ng/L. As ground water criteria are rounded to one significant figure, the recommended criterion for PFNA is 20 ng/L (0.02 µg/L).

Introduction

Development of an interim specific ground water criterion for PFNA was requested of the NJDEP Office of Science by the NJDEP Site Remediation Program. Interim specific ground water criteria are intended to be protective for chronic drinking water exposure.

Background

Perfluorononanoic acid (PFNA, C9) is a member of the class of chemicals called perfluorinated compounds (PFCs). These chemicals have many industrial and commercial uses, are chemically non-reactive, and do not degrade in the environment. Because they are water soluble, they can contaminate surface water and ground water used as drinking water sources. They are not removed from drinking water by conventional treatment processes, but can be removed by granular activated carbon or reverse osmosis and possibly other non-standard treatment processes.

PFNA has been found less frequently and at lower concentrations than the more well-known PFCs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), in drinking water studies from the U.S. and around the world. Drinking water levels (up to 72 ng/L and 150 ng/L) in wells of two public water supplies in Gloucester County, NJ were higher than reported elsewhere in the world. PFNA has also been recently found at lower levels (up to 56 ng/L) in wells of several other Gloucester County public water supplies. PFNA in these wells is believed to result from past releases from a Gloucester County industrial facility.

In contrast to these detections in Gloucester County, PFNA was found (at 20 ng/L or above) in only two public water supplies outside of Gloucester County among 1470 public drinking water supplies nationwide that have reported results of the ongoing PFC monitoring required by the USEPA Unregulated Contaminant Monitoring Rule 3 through January 2014. To our knowledge, no previous situations of drinking water contamination by industrial release of PFNA have been reported prior to the current investigation in Gloucester County.

Human Exposures

Some sources of human exposure to PFCs include food, consumer products, house dust, and drinking water. PFNA is one of four biologically persistent PFCs (PFNA, PFOA, PFOS, perfluorohexane sulfonic acid (PFHxS)) found in the blood serum of almost all U.S. residents. PFNA is found at lower levels in the U.S. population than these other PFCs. However, serum PFNA levels have been increasing over time, while the levels of the other three PFCs are stable or decreasing. PFNA in human serum is believed to result from exposure to PFNA itself and from precursor compounds that can be converted to PFNA in the body. Because PFNA bioaccumulates in fish, recreationally caught fish from contaminated waters are a potential exposure route.

Like other biologically persistent PFCs, PFNA is transferred from the pregnant mother to the fetus and is found in human breast milk. Exposure of infants and young children to PFCs and other contaminants in drinking water is higher than in adults who ingest the same drinking water because infants and young children drink more fluid on a body weight basis than adults.

Toxicokinetics

PFNA is absorbed after oral or inhalation exposure. Like other PFCs, it is chemically non-reactive and is not metabolized. PFNA is distributed primarily to serum, kidney, and liver. In the serum, PFNA is almost totally bound to albumin and other proteins. PFNA is excreted in the urine and feces.

PFNA and PFOA exhibit the same toxicokinetic pattern of persistence in male and female mice and in male rats, with much more rapid elimination of both of these PFCs in female rats. However, the half-life for PFNA is several-fold greater than that of PFOA in males and females of both mice and rats.

PFNA, as well as PFOA, PFOS, and PFHxS, persists in humans with a half-life of several years. Human half-lives for PFOA, PFOS, and PFHxS, have been estimated from data on declines in serum levels after exposures ended, but no such data are available for PFNA. Data on the human half-life of PFNA are limited to a recent study of urinary clearance of PFNA and other PFCs. Although half-lives estimated by urinary clearance are less definitive than those based on serum level declines, these data indicate that PFNA is more persistent in humans than PFOA, consistent with the toxicokinetic data for these two compounds from rodents.

Because of large differences in the half-lives of PFCs between animals and humans, comparisons between humans and animals are made on the basis of internal dose (blood serum levels) rather than administered dose (e.g., mg/kg/day). The ratio between concentration of a persistent PFC in blood serum and drinking water reflects the half-life of the PFC. As discussed below, ongoing exposure to PFOA in drinking water increases human serum PFOA levels by a factor of 100 or greater, so that the serum:drinking water concentration ratio is 100:1 or greater, on average. Data on the relative half-lives of PFNA and PFOA in animals and humans supports an estimated serum:drinking water ratio of 200:1 for PFNA.

Health Effects

Animal Toxicology

PFNA has a toxicity profile similar to that of the closely related compound, PFOA. However, PFNA is generally more toxic and more biologically persistent than PFOA.

Some of the toxicology studies for PFNA, including the study that is the basis for the quantitative risk assessment, used the pure compound, while other studies that provide supporting evidence used a technical mixture of PFCs (Surflon S-111) consisting of 74% PFNA, 20% perfluoroundecanoic acid (C11), and minor amounts of PFOA and C13. Available information, discussed in detail in the draft Technical Support Document, suggests that the effects seen in the technical mixture studies are primarily attributable to PFNA.

In studies of adult rodents, PFNA caused decreased body weight; toxicity to the liver, kidney, immune system, and male reproductive system; hematological effects; and increased serum glucose and related metabolic effects. Many of these effects occurred at the lowest dose tested. As discussed in detail in the draft Technical Support Document, the data indicate that additional and/or more severe effects may occur as exposure duration increases.

When mice were exposed to PFNA throughout pregnancy, severe maternal toxicity occurred at 10 mg/kg/day and neonatal death occurred at 5 mg/kg/day. Developmental effects at the lower doses (1 and 3 mg/kg/day) included decreased weight gain, delayed developmental milestones, and increased liver weight; a No Adverse Effect Level (NOAEL) was not identified for these effects. Increased liver weight and decreased body weight resulting from gestational and/or breast milk exposure persisted in the offspring until the last time point assessed (10 weeks and 9 months, respectively), long after most or all of the PFNA had been eliminated from the body.

Many of the effects of PFNA seen in animals have also been observed in studies of other PFCs. A single dose (<1 mg) of other biologically persistent PFCs to neonatal mice caused permanent neurobehavioral effects accompanied by changes in levels of critical brain proteins. However, PFNA has not been tested for these effects. Similarly, PFNA has not been evaluated for the effects on mammary gland development caused by low doses of PFOA in mice. The structural and toxicological similarity of PFNA to these other PFCs suggests that PFNA may also cause such effects.

There are no chronic toxicology studies for cancer or other effects that may occur from long exposures and/or in old age for PFNA. PFOA and PFOS, the only two PFCs with chronic studies, caused tumors in rats.

Human Epidemiology

In the general population (the NHANES study population in the U.S., and similar populations in other countries), associations have been reported between blood serum PFNA levels and increased cholesterol in adults, increased serum glucose and related parameters in adolescents, diabetes in the elderly, decreased response to rubella vaccine in children, and increased thyroid hormone levels in children. Some of these effects are consistent with effects seen in animal studies. Some of the effects linked with PFNA exposure were not associated with exposure to other PFCs. For some other endpoints, the PFNA effects appear to occur at lower serum concentrations than for other PFCs. Causality cannot be established from these epidemiologic studies because they have a cross-sectional study design A more comprehensive review of both statistically significant and insignificant findings from studies investigating associations of PFNA with health endpoints will be presented in the draft Technical Support Document.

Human populations with elevated exposures to PFNA from drinking water or other environmental media have not been studied. The sole study of workers with occupational exposure evaluated only clinical parameters in blood and is of limited utility, in part because PFNA serum levels were not reported. Additionally, there are no human studies of some important health endpoints, including cancer, that have been linked in epidemiology studies to the closely related PFC, PFOA, in communities with drinking water exposure.

In vitro studies

In *in vitro* studies of a series of PFCs in cultured cells, PFNA was the most potent activator of human and mouse peroxisome proliferator-activated receptor-alpha (PPAR-α), a nuclear receptor believed to be involved in many of the toxic effects caused by PFCs.

Development of Interim Specific Groundwater Criterion

The interim specific groundwater criterion is intended to be protective for chronic (lifetime) exposure through drinking water. It based on the general approach used to develop the New Jersey health-based drinking water guidance for PFOA described in NJDEP (2007) and Post et al. (2009). This approach is applicable to the human health risk assessment of other persistent PFCs (e.g., PFNA) found in drinking water.

The criterion is based on quantitative dose-response modeling of increased maternal liver weight in a mouse developmental study (Lau et al., 2009) conducted by USEPA. In this study, PFNA was administered to pregnant mice during gestation days 1-16. Increased liver weight is a well-established effect of PFNA and other PFCs in experimental animals. This study and endpoint were selected because the serum levels needed for dose-response modeling were provided. Benchmark dose modeling was used to determine the BMDL (i.e., the lower confidence level of the benchmark dose, which is the PFNA serum level causing a 10% increase in liver weight) serum concentration of 5,200 ng/ml.

Modeling of endpoints for developmental toxicity in the offspring in Lau et al. (2009) gave similar results (i.e., BMDL values) to those obtained for maternal liver weight. These developmental endpoints were not used as the basis for quantitative dose response modeling because of greater uncertainty regarding the temporal relationship between the times at which PFNA was measured in maternal serum and the times at which these effects were assessed in neonates. A number of studies from other laboratories showed other types of toxicity at similar dose levels and exposure durations, but did not provide the serum level information needed for modeling. These additional data provide qualitative support for the criterion based on the increased maternal liver weight in Lau et al. (2009).

A total uncertainty factor of 300 was applied to the BMDL of 5,200 ng/ml PFNA serum concentration for increased maternal liver weight. This consisted of the following individual factors: 3 for toxicodynamic differences between humans and animals; 10 for protection of sensitive human subpopulations; and 10 for extrapolation from the short-term study to protect for effects which could occur from chronic exposure and for gaps in the toxicology database for PFNA. The resulting target human serum level expected to be protective for chronic exposure is 17 ng/ml (17,000 ng/L or 17 µg/L, ppb).

Application of the Relative Source Contribution of 20% that accounts for non-drinking water exposures when developing interim specific ground water quality criteria results in a target human serum level from drinking water exposure of 3.4 ng/ml (3,400 ng/L).

Based on the assumed 200:1 ratio between PFNA serum and drinking water concentrations with chronic ingestion, the drinking water concentration resulting in a target human serum level of 3.4 ng/ml (3,400 ng/L) is 17 ng/L.

Using default assumptions for derivation of interim specific groundwater criteria for a non-carcinogen, the Reference Dose that support the derivation of a criterion of 17 ng/L is 2.42 ng/kg/day, as follows:

$$\frac{17 \text{ ng/L} \times 2 \text{ L/day}}{70 \text{ kg} \times 0.2} = 2.42 \text{ ng/kg/day}$$

And:

$$\frac{2.42 \text{ ng/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 17 \text{ ng/L}$$

Where: 17 ng/L = Interim specific groundwater criterion
70 kg = Average adult body weight
2 L/day = Assumed daily water consumption
0.2 = Relative Source Contribution factor.

As interim ground water criteria are rounded to one significant figure, the recommended criterion for PFNA is 20 ng/L (0.02 µg/L).

Key Uncertainties

- Ongoing exposure to PFNA at 20 ng/L (0.02 µg/L) in drinking water is estimated to contribute an additional 4 ng/ml, on average, to the PFNA concentration in blood serum already present in the general population. Thus, the average serum level in communities with drinking water at this concentration is estimated at about 5.5 ng/ml, 3.7-fold higher than the average serum level of about 1.5 ng/ml in the adult general population (who are assumed to have no drinking water exposure). A serum level of 5.5 ng/ml is well above the 95th percentile PFNA serum level of 4.0 ng/ml in the adult U.S. general population. In infants and children, serum levels from ongoing exposure to 20 ng/L PFNA in drinking water would possibly be greater than in adults, due to their greater water consumption on a body weight basis. Several potentially important health endpoints have been associated with PFNA in the human general population exposure range, although it is not clear whether these associations reflect causality. Thus, there is uncertainty about the extent of protection provided by a criterion that will result in serum PFNA levels several-fold above the general population range.

- There have been no human studies of communities with exposures to PFNA from contaminated drinking water or other environmental media. Thus, there is no information on health effects which may occur in communities with exposures higher than in the general population.

- Some important health endpoints, including cancer, that have been linked in epidemiology studies to PFOA, a PFC that is closely related to PFNA, have not been evaluated in humans exposed to PFNA.

- There are no chronic toxicology studies of cancer or other effects that may occur from long exposures and/or in old age. PFOA and PFOS, the only two PFCs with chronic studies, caused tumors in rats.

- PFNA has not been tested for specific effects seen from low doses of PFOA and/or other PFCs including neurobehavioral effects after a single dose to neonatal mice and delayed mammary gland development from low dose developmental exposures. It is not known whether PFNA causes these effects.

- The mouse developmental study used as the basis for the interim specific criterion did not evaluate histopathological (microscopic) changes in the liver. Histopathological changes in the liver were seen at a lower dose in the two-generation rat study of the mixture of PFCs consisting primarily of PFNA. Although there is uncertainty about the contribution of the other PFCs, the data suggest that PFNA was primarily

responsible for the toxicity seen in this study. The two-generation study cannot be used as the basis for quantitative risk assessment because the quantitative serum PFNA data are not available. However, the graphical presentation of the serum levels from this and an accompanying subchronic study suggest that histopathological changes in the liver occurred at lower serum levels than in the mouse developmental study that was used for risk assessment. The uncertainty factor of 10 for short- to longer- duration of exposure is expected to be protective for these effects.

- Uncertainties about the human relevance of effects seen in animals are inherent to all risk assessments based on animal data. As discussed in detail in the draft Technical Support Document, available information indicates that it is appropriate to consider effects of PFNA observed in experimental animals to be relevant to humans for the purposes of risk assessment.

- There is uncertainty about the assumed 200:1 ratio between serum and drinking water for PFNA that is used in this assessment. A 100:1 or greater ratio between serum and drinking water for ongoing exposure to PFOA has been well established. Toxicokinetic data show that the half-life of PFNA is several- fold greater than that of PFOA in rodents, and limited human half-life data based on renal clearance indicates a longer human half-life for PFNA than PFOA. Although upper percentile values for exposure parameters are typically used in risk assessment, it should be noted that the serum:drinking water ratio for PFNA of 200:1 is intended to represent a central tendency estimate, not an upper percentile value, for this ratio.

- The USEPA study used as the quantitative basis for the derivation of the interim specific criterion (Lau et al., 2009) was presented at the Annual Meeting of the Society of Toxicology in 2009 and is expected to be published in a peer reviewed journal in the near future. The PFNA serum level and maternal liver weight data used to develop the interim ground water criterion were presented graphically by Lau et al. (2009) and were obtained in numerical form from Dr. Lau (personal communication). They are final data and are not expected to change in the published version of this study.

- Available information discussed in the draft Technical Support Document indicates that the target organs and modes of action are similar for PFNA and other PFCs, particularly PFOA. Therefore, the toxicity of PFNA and other PFCs may be additive. Although PFNA and other PFCs, including PFOA, are known to co-occur in some NJ public water supplies, the potential for additive toxicity of PFNA and other PFCs was not considered.