ERRATA SHEET

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NJDEP RESPONSE SUMMARY ON REQUEST FOR PUBLIC INPUT ON THE DRAFT INTERIM SPECIFIC GROUND WATER QUALITY CRITERION AND DRAFT PRACTICAL QUANTITATION LEVEL FOR PERFLUORONONANOIC ACID (PFNA)

Page	Paragraph	Correction
12	2nd Response (5th paragraph) (last sentence)	Changed “sufficient” to “insufficient”

NJDEP RESPONSE SUMMARY ON REQUEST FOR PUBLIC INPUT ON THE DRAFT INTERIM SPECIFIC GROUND WATER QUALITY CRITERION AND DRAFT PRACTICAL QUANTITATION LEVEL FOR PERFLUORONONANOIC ACID (PFNA)

On March 14, 2014 the New Jersey Department of Environmental Protection (NJDEP) requested public input on two documents, the draft interim specific ground water quality criterion and the draft practical quantitation level for perfluorononanoic acid (PFNA). Comments were requested by April 21, 2014. Based on requests for an extension of the comment period this was extended to May 1, 2014.

The public was requested to provide input on the following focus issues:

Draft Interim Practical Quantitation Level (PQL):

1. Are you aware of additional data or technical information concerning analytical methods to detect PFNA that would affect the selected draft Interim PQL?

Draft Interim Specific Ground Water Quality Criterion:

1. Are you aware of additional data or technical information concerning the toxicology, epidemiology, toxicokinetics, or other studies related to health effects of PFNA that should be considered in the development of the criterion?
2. Is the document factually accurate, e.g., are the data sources correctly cited; are the calculations correct?
3. Is the factor used to relate PFNA intake in drinking water to PFNA concentrations in human serum reasonable and appropriate for the development of the ground water criterion?
4. Is the choice of study and toxicological endpoint used as the quantitative basis for development of the criterion (i.e., maternal liver weight increase in a mouse developmental study) appropriate?
5. Have the key uncertainties in this assessment been identified and appropriately characterized? Have the uncertainty factors been applied appropriately? Are you aware of any additional data that would inform the uncertainties listed in this document?

Subsequently, on April 9, 2015, the New Jersey Department of Environmental Protection requested public input on revisions for two factors (Uncertainty Factors and Relative Source Contribution factor) used in the development of the draft Interim Specific Ground Water Quality Criterion (ISGWQC) for Perfluorononanoic Acid (PFNA, CAS # 375-95-1) that was posted for public comment on April 17, 2014.

The public was requested to provide input on the following focus issues:

1. Are you aware of additional data or technical information relevant to the choice of uncertainty factors?
2. Are the uncertainty factors consistent with current USEPA guidance and the use of uncertainty factors in previous risk assessments developed by USEPA, NJDEP, and DWQI?
3. Are you aware of additional data or technical information relevant to the choice of Relative Source Contribution factor?

4. Is the Relative Source Contribution factor consistent with current USEPA guidance and the use of uncertainty factors in previous risk assessments developed by USEPA, NJDEP, and DWQI?

Summary of Public Comments on Draft PFNA Documents

March 14, 2014 request for public input: Eleven sets of comments were received. The comments fall into four general categories: legal/policy/process, technical basis for PQL, technical basis for interim criterion and concerned citizen. Some submittals included comments in more than one of the four general categories.

April 9, 2015 request for public input: Four sets of comments were received. All of the submittals addressed the two factors used in the derivation of the Interim Specific Ground Water Criterion that had been revised. One of these submittals included comments submitted to the Drinking Water Quality Institute on its three draft reports (Health-based MCL, Practical Quantitation Level, and Treatment). Many of these comments address topics other than the two factors that were revised, and some of these comments are not relevant to the draft Interim Specific Ground Water Quality Criterion Technical Support Document or the draft Practical Quantitation Level Technical Support Document. For this submittal, comments on issues other than the two revised factors were considered if relevant to the draft Interim Specific Ground Water Quality Criterion and Practical Quantitation Level documents. Comments relating to the Drinking Water Quality Institute draft reports that are not relevant to the NJDEP documents were not considered.

In the comments and responses below, comments received in response to the March 14, 2014 request for public comment are noted as "2014" and those received in response to the April 9, 2015 are noted as "2015".

NJDEP Response

Legal/Policy/Process (2014): Five (5) submittals contained comments relating to legal, policy, and/or process issues.

Response: The New Jersey Department of Environmental Protection (the "Department") has authority to regulate ground water. N.J.A.C. 7:9C-1.7. When a contaminant not currently regulated is identified, the Department may create interim specific ground water quality criteria ("ISGWQC") based upon the weight of the evidence available regarding the contaminant's carcinogenicity, toxicity, public welfare or organoleptic effects, as appropriate for the protection of potable water. N.J.A.C. 7:9C-1.7(c)(2-3). Sufficient evidence exists regarding PFNA's adverse impacts to warrant the Department's creation of an ISGWQC. While public comment is not a requirement for the establishment of an ISGWQC, the Department elicited comments from the public in both 2014 and 2015. Additionally, the matter was researched and addressed in open session in June 4, 2015 by the Drinking Quality Water Institute (DQWI). The Department

considered DQWI's findings and incorporated its recommendation. The Department considers both public mechanisms consistent with the principles of Executive Order No. 2.

An ISGWQC must be replaced by specific criteria as soon as reasonably possible. N.J.A.C. 7:9C-1.7(c)(2)(ii). If the Department wishes to promulgate a Maximum Contaminant Level (MCL) for a contaminant, it must follow rulemaking procedures. Such procedures include: 30-days notice prior to implementation, summary of the proposed regulation in the New Jersey Register, and 30-day public comment period. N.J.S.A. § 52:14B-4(a). Therefore, members of the public will have additional opportunity to provide comments on the matter prior to the establishment of a MCL. While the Department has complied with the principles of Executive Order No. 2 in its process to date, the process for establishing the MCL is also aligned with the principles of Executive Order No. 2, allowing additional public input.

Additional information can be found at: *http://www.state.nj.us/dep/wms/bwqsa/gwqs.htm*

In addition, the Department has requested that the Drinking Water Quality Institute develop recommendations for maximum contaminant levels (MCLs) for drinking water for three perfluorinated chemicals (PFCs) including PFNA. Additional information can be found at: http://www.nj.gov/dep/watersupply/g_boards_dwqi.html

Technical Basis for Draft Practical Quantitation Level (PQL):

Comment (2014): One commenter stated that the method used to develop a practical quantitation level (PQL) is not in accordance with NJAC 7:9C-1.9 c 3. It is unclear how a reliable outcome using the bootstrap method was obtained if the Department used a very small sample size. Furthermore Method Detection Levels (MDLs) from the three laboratories certified for NJDEP for PFC analysis are quite variable for PFNA. The results are unlikely to be achievable in many cases.

*Respons*e: The Department followed the method in accordance with NJAC 7:9C-1.9c3. The proposed PQL for the draft Interim Specific Ground Water Quality Standard for PFNA used a literature review process and consideration of performance data on analytical capability for interim standards. It is consistent with the process that is routinely used to develop practical quantitation level (PQLs) for Interim Specific Ground Water Standards, as documented in Ground Water Quality Standards at http://www.nj.gov/dep/rules/rules/njac7_9c.pdf

The regulatory citation is as follows:

3. Selection and derivation of PQLs shall be as follows:
   i. PQLs shall be rounded to one significant figure using standard methods.
   ii. PQLs listed in Appendix Table 1 were, and additional PQLs shall be, derived or selected for each constituent using the most sensitive analytical method providing positive constituent identification from (c)3ii (1) and (2) below, in that order of preference:

   (1) PQLs derived from Method Detection Limit (MDL) data from the New Jersey Department of Health and Senior Services Laboratory (DHSS) multiplied by 5;

Note: The New Jersey Department of Health and Senior Services Laboratory (DHSS) is not certified for this parameter and therefore is not an option.

(2) PQLs derived from laboratory performance data that has been evaluated by the Department using the method of Sanders, Lippincott and Eaton (See Sanders, P. et al., "Determining Quantitation Levels for Regulatory Purposes." J. Amer. Water Works Assoc., 1996, March pp. 104-114).

Response: This second option was the process used to calculate the draft PQL. The procedure was augmented by a new statistical procedure utilized by USEPA to generate reporting limits. This procedure has the advantage of generating an Upper Control Limit which is compared to the PQL as additional evidence of laboratory capability for the parameter of interest.

It should be noted that the information presented by the commenter for the Method Detection Levels (MDLs) for the Laboratory Standards Operating Procedures (SOPs) from Eurofins Eaton and Test America are representative of the capabilities of those laboratories, based on an extensive dataset for PFCs in ground water/drinking water submitted by those laboratories to NJDEP over the past several years. The data reviewed by NJDEP indicates that the proposed practical quantitation level (PQL) is generally achievable by commercial laboratories.

Technical Basis for Draft Interim Criterion:

Summary: Eight of the eleven 2014 commenters and all four of the 2015 commenters provided comments on the scientific basis for the draft Interim Specific Ground Water Criterion.

No information was submitted that resulted in a change in the general approach used for the risk assessment, the choice of study used for quantitative risk assessment, or the value for the Interim Specific Ground Water Criterion.

Focus Question 1 (2014): Are you aware of additional data or technical information concerning the toxicology, epidemiology, toxicokinetics, or other studies related to health effects of PFNA that should be considered in the development of the criterion?

Comment (2014): One commenter provided citations for seven additional epidemiology studies that evaluated associations of health effects with PFCs including PFNA.

Response: Summaries of six of these studies are included in the revised document. The seventh study, Yeung et al. (2013), was not considered relevant. It evaluated the distribution of PFCs between liver and serum in patients who had received liver transplants due to a variety of liver diseases (cancer, cirrhosis, hepatitis, and others) as compared to the serum/liver distribution in individuals without liver disease.

Focus Question 2 (2014): Is the document factually accurate, e.g., are the data sources correctly cited; are the calculations correct?

Comments (2014): One commenter noted that the half-life data for male and female mice were reversed in Table 1, and that the information for Footnote c was missing in Table 1. Another

commenter noted the need for clarification of the summary paragraph on epidemiology studies related to diabetes.

Response: These corrections and clarifications have been made. These revisions do not affect the overall conclusions in the document.

Comments (2015): One commenter submitted comments on the Benchmark Dose modeling used to derive the point of departure for the risk assessment and said it was not consistent with EPA guidance on Benchmark Dose modeling. The commenter stated that the standard errors shown in the output of the Benchmark Dose modeling of increased maternal liver weight from Das et al. (2015) does not match the standard errors for the serum PFNA data for the pregnant mice in this study. The commenter questioned the use of a serum level of zero for the control group in the modeling since the serum level was actually 0.015 ug/ml. They also questioned the selection of a model for which the p value cannot be calculated. They stated that appropriate quality control processes were not used in conducting and reporting the Benchmark Dose modeling and that the statistical parameters generated by the Benchmark Dose modeling were not completely presented.

Response: The commenter apparently did not realize that the standard errors and the standard deviations used in the BMD modeling are for the outcome (liver weight), not for PFNA serum levels (the dose metric). The standard errors for the PFNA serum levels are not used in the BMD modeling.

Subsequent to the posting of the March 2014 Technical Support Document, the Office of Science was informed by the investigators for the Das et al. (2015) study that data for one or two animals with full litter resorptions in each dose group had been inadvertently included in the serum PFNA data that had been provided. The value for the number of animals in one dose group had also been transcribed incorrectly in the earlier BMD modeling.

The individual animal data for liver weight and PFNA serum concentration in the pregnant animals on GD 17 were provided by the investigator, and these data were used by the Office of Science to independently verify the means and standard deviations for the BMD modeling. BMD modeling for a 10% increase in maternal liver weight was conducted using the corrected serum data (with the data from the animals with full litter resorptions removed), and the corrected value for number of animals in the 5 mg/kg/day dose group, using a more recent version of the EPA BMD software (version 2.6.0.86). All models for continuous data included in the software were run. The results of the new BMD modeling are close to, but slightly different, than the earlier results.

The Hill model and the Exponential model 5 gave almost identical AIC statistics, and these were the lowest AIC values of the models run. Both of these models had small scaled residual values for the dose closest to the BMD and also show an excellent visual fit to the data. For these reasons, the average of the BMDLs from these two models are used as the Point of Departure. The BMDLs for the Exponential model 5 and the Hill model are 4.43 µg/ml and 5.43 µg/ml, respectively. The average of these values is 4.93 µg/ml, which rounds to 4.9 µg/ml, slightly lower than the earlier BMDL of 5.2 µg/ml. This minor change in the BMDL did not affect the value of the draft Interim Specific Ground Water Criterion.

The use of zero for the serum concentration in the control group in the previous analysis had no practical effect on the outcome. Nevertheless, the actual value, 0.013 µg/ml, was used instead of zero in the new BMD modeling.

Regarding the use of models for which a p value cannot be calculated, the BMDS software provides two model-based measures of the fit of a given model to the observed data, the chi-squared goodness-of-fit test (the "p" value referred to in the comment) and the AIC statistic. As the commenter states, the chi-squared p statistic is a global measure of fit. The AIC statistic, on the other hand, reflects both goodness of fit and parsimony of fit. The inability of the BMDS software to calculate the p-value for the Hill model, and (in our revised benchmark dose calculation), the exponential model 5 model merely means that the degrees of freedom for the fitted model (e.g. the Hill model) and the "full" model that are compared in test 4 of the BMDS output are identical. This does not reflect one way or the other on the suitability of the fit of the given model. In this case, one can still make a good determination of the model fit from the AIC statistic, the scaled residual (particularly for the dose closest to the BMD), and from a visual assessment of the graphical fit of the model. In the case of both the Hill and Exponential-5 models, the AIC statistic (essentially identical for both models) is quite small, as are the scaled residuals. Visual examination of the graphical fit shows that both models fit the data nearly perfectly. We are, therefore, confident that both of these models provide a more than adequate fit of the data and that the resulting BMDs and BMDLs are appropriate.

Regarding completeness of presentation of information related to BMD modeling, outputs of all BMD models that were run are included in an Appendix in the final document. Additionally, a complete table that includes the results of all of the models run, including the parameters in the tables presented by the commenters (above) are included. It will certainly be possible to easily replicate the BMD modeling presented in the final document.

Focus Question 3 (2014): Is the factor used to relate PFNA intake in drinking water to PFNA concentrations in human serum reasonable and appropriate for the development of the ground water criterion?

Comments: One commenter stated that the presentation of the basis for the factor was generally well done. The commenter stated that the uncertainties related to the factor were acknowledged, that the EPA approach to assessing human exposure to PFCs from drinking water also has uncertainties, and that one cannot conclude whether the NJDEP or EPA approach is better.

Three commenters noted that the serum:drinking water ratio can vary among individuals. Two of these commenters noted that 200:1 represents a central tendency estimate and that higher ratios are expected in many individuals. Thus, the 200:1 ratio may underestimate risk. The third commenter stated that a large range of uncertainty is associated with the ratio, and that it did not undergo an appropriate level of scientific review.

Another commenter stated that assumptions used in the kinetic model of Clewell (2006:2009) which supports the 100:1 ratio for perfluorooctanoic acid (PFOA) need to be more closely examined and that no model is available for PFNA. The commenter noted that there are no empirical data on serum levels from drinking water exposure, and that the human half-life

estimates for PFNA are based on a single renal clearance study with very variable and uncertain results.

Response: The inter-individual range of the serum:drinking water ratio and the fact that the 200:1 ratio represents a central tendency, rather than an upper percentile value, are discussed in detail in the draft document. The uncertainties in the estimates of human half-life of PFNA from the renal clearance study were acknowledged in the draft document. As discussed in the draft document, based on the kinetic data from rats, mice, and humans (Tables 1 and 2), it is reasonable and not overly conservative to assume a 200:1 ratio for PFNA.

Comment (2015): One commenter disagreed with the use of a central tendency (median) value for the serum:drinking water ratio and mentioned that the half-life of PFOA is higher in children. The commenter stated that use of the central tendency estimate of 200:1 is inconsistent with upper percentile exposure values used by USEPA and is a less protective and non-conservative ratio. Another commenter stated that the 200:1 ratio for PFNA is based on extrapolation from other perfluorinated compounds and lacks supporting data and specificity.

*Response***:** The 200:1 ratio is an estimate supported by available animal data and limited human data. As stated by the first commenter, it is intended to represent a central tendency, not an upper percentile, value. There is no basis for development of an upper percentile estimate for this factor. We are confident that the Interim Ground Water Quality Criterion based on the 200:1 ratio is sufficiently protective.

Comments (2015): Two commenters submitted comments based on the assumption that the 100:1 serum:drinking water for PFOA does not consider non-drinking water source of exposure. One of the commenters also believed that the 100:1 ratio for PFOA based only on the Emmett et al. (2006) study of a community with very high concentrations (>3 µg/L) concentrations of PFOA in drinking water and did not consider individuals exposed to lower concentrations of PFOA in drinking water.

Response: These comments are not factually correct and are based on misunderstanding of the basis of the 100:1 serum:drinking water ratio for PFOA. Both commenters were apparently unaware that Post et al. (2009; excerpt below) considered the contributions of non-water exposures when developing the 100:1 serum: drinking water ratio for PFOA. Furthermore, the 100:1 serum:drinking water ratio for PFOA is not based only on the Emmett et al. (2006) study of a community with very high (>3 µg/L) levels of PFOA in their drinking water. As discussed in Post et al. (2009; excerpt below) it is based on data from communities with a range of drinking water concentrations (60 – 4300 ng/L) in Ohio and West Virginia, and it is further supported by a number of other studies from other locations as well as several modeling efforts, all of which are cited in the Technical Support document.

> From Post et al. (2009): *For lower drinking water concentrations, nonwater sources are likely to contribute a greater proportion of the PFOA in the blood than in those using highly contaminated water. To find a lower bound on the ratio of serum to water PFOA concentrations, it can be assumed that none of the U.S. background serum concentration of about 4 µg/L results from drinking water. If this serum concentration of 4 µg/L is subtracted from the median serum concentration for*

Village of Pomeroy (12 µg/L), the ratio of the remaining serum concentration (8 µg/L) to the drinking water concentration (0.065 µg/L) is 123:1. Therefore, PFOA appears to concentrate in serum of people exposed to lower drinking water concentrations in a similar ratio to that reported in a highly exposed community (16).

4. Is the choice of study and toxicological endpoint used as the quantitative basis for development of the criterion (i.e., maternal liver weight increase in a mouse developmental study) appropriate?

Comments (2014): One commenter stated that the risk assessment was consistent with data that they had reviewed, but that they had not reviewed the study used as the quantitative basis for the risk assessment. Another commenter said that the choice of study was generally well done and was a reasonable balance between studies that found effects in liver and other animal studies finding effects at lower doses, but that the basis should be frequently reviewed due to current level of research interest in PFCs. This commenter also suggested consideration of data for PFOA in the evaluation of PFNA including toxicological effects at low doses that have not been evaluated for PFNA (such as delayed mammary gland development), chronic data showing that PFOA causes tumors in rats, and the extensive epidemiology database for PFOA. It was noted that there is some suggestion of increased breast cancer from PFOA in individuals with certain genetic variants. It was suggested that consideration should be given to the fact that chronic exposure to drinking water at the proposed criterion level will elevate serum levels close to those associated with human health effects.

Response: The PFOA studies mentioned by the commenter include low dose toxicological effects for endpoints which have not been evaluated in PFNA, tumors in chronic PFOA rat studies (while no chronic data for PFNA are available), and the extensive epidemiology database including communities with exposure to PFOA from contaminated drinking water (while no such data are available for PFNA). These three types of studies of PFOA are discussed in the draft document and are considered in the Discussion of Uncertainties in the draft document.

Comments (2014): Four commenters stated that the interim criterion should not be based on a study that has not yet been peer reviewed and published, and that important information about the study design and results is not provided in the abstract and the poster. One commenter also noted that the raw data for Benchmark Dose modeling were not provided in the draft document.

Response: The study used as the basis for the risk assessment has subsequently been published in a peer reviewed journal (Das, K.P., Grey, B.E., Rosen, M.B., Wood, C.R., Tatum-Gibbs, K.R., Zehr, R.D., Strynar, M.J., Lindstrom, A.B., Lau, C. (2015). *Developmental toxicity of perfluorononanoic acid in mice*. Reproductive Toxicology 51:133-144). The data used for Benchmark Dose modeling were the numerical data for results presented in bar graphs in the publication and were provided by Dr. Lau. See response above concerning the Benchmark Dose modeling.

Comment (2014): One commenter stated that the liver weight data from peroxisome proliferator activated receptor-alpha (PPAR-alpha) null mice (knock out mice) from Wolf et al. (2010) more accurately represent human liver response than the Lau et al. (2009) data from CD-1 mice, and that liver weight was less affected in the knock out mice. They stated that the human relevance

of the mouse model due to differences between human and mouse PPAR-alpha receptors was not adequately addressed. Another commenter stated that liver weight occurred at lower doses in non-pregnant mice than in pregnant mice in Wolf et al. (2010), while in Lau et al. (2009), liver weight increases were more pronounced in pregnant than non-pregnant mice, although serum levels are higher in non-pregnant mice at each dose. The reliability and relevance of liver weight change in non-pregnant mice in Lau et al. (2009) as the basis for criterion was questioned.

Response: As indicated by its title, "Developmental Effects of Perfluorononanoic Acid in the Mouse Are Dependent on Peroxisome Proliferator-Activated Receptor-Alpha", a primary focus of Wolf et al. (2010) was developmental effects. In regard to human relevance of PPAR-alpha mediated effects in general, Wolf et al. (2010) state: "Relevance of the PPARα mechanism to humans has been criticized primarily based on the lower number of these receptors in the liver of human versus mouse. However, PPARα is implicated here in the developmental effects of PFNA as well, and the etiology of PPARα in other tissues of the embryo, fetus and neonate of the human and the mouse that are involved in gross development has not been fully determined. Therefore, the possibility of relevance of PPARα to a human response to PFNA cannot be dismissed."

The liver weights and serum levels in Wolf et al. (2010) were measured on postnatal day 21, a time point that is 23 days after the last dose of PFNA. The "pregnant" mice are more appropriately referred to as "mice that had given birth (and nursed for 21 days)". In these mice that had given birth 21 days earlier and nursed the pups until weaning on postnatal day 21, much of the PFNA would have been eliminated by excretion in the milk by postnatal day 21. Interpretation of the liver weight and serum data is complicated by the fact that these parameters were assessed long after dosing ended, and because delivery and nursing of pups would have affected serum PFNA levels and likely liver weight in the mice that had given birth. Therefore, the Wolf et al. (2010) data are not appropriate for use as the quantitative basis for the PFNA criterion.

In contrast, Lau et al. (2009) measured liver weights one day after dosing ended and before nursing of the pups began, a time point which reflects the effects of the administered PFNA. The difference in time points at which serum levels and liver weights were assessed in the two studies would affect the serum PFNA levels and the liver weight increases, precluding comparisons of relative serum levels and liver weight effects between the two studies in pregnant mice/mice that had given birth and non-pregnant mice.

Additionally, as discussed in the draft document, liver weights were increased by PFNA in both wild type and knock out non-pregnant mice 23 days after the last dose of PFNA. However, in the mice that had given birth, liver weight was increased in the wild type, but not the knock out mice, 23 days after giving birth. It is important to note that, in mice that had given birth, PFNA serum levels in the knock out mice were much lower than in the wild type mice for a reason that was not determined. The No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) for increased liver weight based on serum levels are consistent in the WT and knock out mice, suggesting that the difference in response is likely due to kinetic differences unrelated to PPAR-alpha status.

Because the initial draft criterion was based on data from pregnant, not non-pregnant mice, from Lau et al. (2009), the intent of the comment on the relevance of effects in non-pregnant mice in this study is not clear.

Comment (2014): A commenter suggested that Lau et al. (2009) should be compared to the Stump et al. (2008), Mertens et al. (2010), and Wolf et al. (2010) as far as kinetic differences in rats and mice, dosing with a mixture of PFCs primarily consisting of PFNA versus pure PFNA, dose ranges, and study durations. It was noted that Fang et al. (2012) reported a No Observed Adverse Effect Level (NOAEL) of 1 mg/kg/day and a Lowest Observed Adverse Effect Level (LOAEL) of 5 mg/kg/day for liver histopathology in rats dosed with PFNA for 14 days, while Stump et al. (2008) and Mertens et al. (2010) found liver histopathology at much lower doses of PFNA as the primary component of a mixture of PFCs, in studies of much longer duration. The uncertainties in the inference that liver histology may have occurred in low dose groups in Lau et al. (2009) and Wolf et al. (2010) should be more clearly qualified.

Response: The design of these studies, including all of the factors mentioned by the commenter, is clearly discussed in the draft document. It should be noted that, because liver weight was not measured in Fang et al. (2012a), the doses that affected liver weight cannot be compared to those that caused histopathological changes.

Comment (2014): One commenter stated that the data from Stump et al. (2008) and Wolf et al. (2010) suggest that PFNA causes increased liver weight in rodents through activation of PPAR-alpha, and that humans are less responsive. It cannot be determined whether a 10% increase in liver weight is an adaptive response or an adverse effect because histopathology was not performed in the study used as the basis for the risk assessment. Increased liver weight is not an indicator of adverse human health effects without evidence of histopathological changes.

Response: In contrast to the commenter's statement, Stump et al. (2008) did not assess PPAR-alpha activation by PFNA. The increased liver weight from PFNA has both PPAR-alpha mediated and non-PPAR alpha mediated components (Wolf et al., 2010). Mertens et al. (2010) found that PFNA is a mild activator of PPAR-alpha, with a maximum increase in hepatic beta-oxidation of 3.1-fold in male rats that was associated with a 1.8 fold increase in relative liver weight. In contrast, for Wyeth 14,643, a model compound for PPAR-alpha activation, an increase in liver weight of similar magnitude (2.1 – 2.4 fold) was associated with an increase in hepatic beta-oxidation of 23-29 fold in rats (Biegel et al., 1992), and Wyeth 14,643 does not increase liver weight in PPAR-alpha knock out mice (Wolf et al., 2008).

Several studies presented in the draft document demonstrate that PFNA causes histopathological effects in the liver, and suggest that these effects may occur at lower doses than those used by Lau et al. (2009). It is important to note that the histopathological changes in the liver reported by Fang et al. (2012), Stump et al. (2008), and Mertens et al. (2010) are not of the same nature as are associated with PPAR-alpha activation (peroxisome proliferation and increased smooth endoplasmic reticulum), suggesting that PFNA causes liver toxicity independent of PPAR-alpha mediated effects. This information, as well as additional discussion of the potential human relevance of PPAR-alpha mediated effects, has been added to the draft document.

Increased liver weight is used as a key endpoint in risk assessment by EPA IRIS and other organizations without histopathological changes necessarily occurring concurrently. In some instances where increased liver weight is the basis for risk assessment, the effect occurred in the absence of histopathological changes in the liver. In other cases, histopathological changes occurred at higher doses than the Lowest Observed Adverse Effect Level (LOAEL) for increased liver weight that was used as the basis for risk assessment.

Comment (2014): One commenter stated that endpoints other than increased liver weight should be considered for human risk assessment. They further stated that a weight of evidence approach based on results of multiple studies was not used, and that studies that did not report serum PFNA concentrations were not considered.

Response: Other studies and endpoints, including those mentioned by the commenter (e.g., body weight, organ weight, triglyceride levels, and testicular toxicity in the studies cited by the commenter), were considered as part of the weight of evidence for effects of PFNA. See "Key and Supporting Studies and Endpoints" section of draft document. The fact that PFNA caused liver effects and other types of effects at similar or lower doses than the Lowest Observed Adverse Effect Level (LOAEL) in the study used as the basis for quantitative risk assessment is clearly explained. As discussed in the draft document, serum PFNA data that would be helpful in interpreting the results of the two industry-sponsored rat studies (Stump et al., 2008 and Mertens et al., 2010) were requested from the study sponsors but were not provided.

Focus Question 5 (2014): Have the key uncertainties in this assessment been identified and appropriately characterized? Have the uncertainty factors been applied appropriately? Are you aware of any additional data that would inform the uncertainties listed in this document?

Focus Questions 1 and 2 (2015): Are you aware of additional data or technical information relevant to the choice of uncertainty factors? Are the uncertainty factors consistent with current USEPA guidance and the use of uncertainty factors in previous risk assessments developed by USEPA, NJDEP, and DWQI?

Comments (2014): One commenter stated that this aspect of the risk assessment was generally well done. Another stated that the uncertainties in 200:1 ratio are acknowledged, that the EPA approach also has uncertainties, and that one cannot conclude which approach is better.

Response: These comments are acknowledged.

Comments (2014): One commenter stated that no basis is provided for an interspecies uncertainty factor of 3 and that the default uncertainty factor of 10 for interspecies variability should be used. Another commenter stated that the interspecies uncertainty factor of 3 for toxicodynamic variability between animals and humans should be removed because responses to PPAR-alpha activation are greater in mice than humans, and that the total uncertainty factor should be reduced from 300 to 100.

Response: As explained in the draft document, it is appropriate to apply an interspecies uncertainly factor of 3 for toxicodynamic variability instead of the default interspecies uncertainty factor of 10. This is because the toxicokinetic variability component of the

uncertainty factor is not used since the interspecies comparison is based on internal dose (serum levels) rather than administered dose. Therefore, the removal of the uncertainty factor of 3 for interspecies toxicodynamic variability is not appropriate. There are many uncertainties about the relative sensitivity of animals and humans to the effects of PFNA, and epidemiology data from the general population suggest that PFNA may cause effects in humans at exposures well below those tested in animal studies.

Comment (2014): One commenter stated that the uncertainty factors for exposure duration and data gaps should not be combined. They recommended that a full uncertainty factor of 10 for duration of exposure and an additional uncertainty factor for data gaps be applied.

Response: This comment is acknowledged. As noted in the draft document, some, but not all, of the data gaps would be addressed by chronic studies of pure PFNA.

Comment (2014): One commenter stated that an uncertainty factor for interspecies kinetic differences should be used instead of serum-based approach, and that use of an administered dose with this uncertainty factor is standard approach for risk assessment. The approach used is more uncertain than the standard approach.

Response: It is generally accepted that interspecies comparison for persistent PFCs such as PFNA must be made on the basis of internal dose (serum level) or another approach that accounts for the large differences in half-lives between humans and experimental animals (Post et al., 2009; Tardiff et al., 2009; USEPA, 2009; USEPA, 2014). It is not appropriate to base the interspecies comparison on administered dose because a given administered dose results in very different internal doses in humans and experimental animals. Application of the default uncertainty factor of 3 is insufficient to account for interspecies toxicokinetic differences for PFCs.

Comment (2014): One commenter listed a number of uncertainties and data gaps (see bullets below).

General Response: Some of the issues mentioned were addressed above and are not repeated here. All of the uncertainties and data gaps listed below are discussed in the draft document. Additional responses to specific issues are noted below.

- *There are little human and animal dose response data based on serum PFNA measurements.*
  Response: The epidemiology studies in the general population provide serum PFNA data, while the single occupational study does not. Attempts to contact the authors of the occupational study to obtain additional data were not successful.
- *There is no kinetic model for extrapolations between species or doses.*
  Response: An approach based on serum levels is used to account for kinetic differences between species and to provide the internal dose associated with a given administered dose.
- *"Excluding toxicity data on the basis of missing serum measurements" reduces the data that can be considered.*
  Response: As discussed above, studies which do not provide serum data are considered in the weight of evidence evaluation, but are not used as the quantitative basis for risk assessment.

- *Timing of serum measurements relative to when dosing ended precludes use of serum data for dose response.*
  Response: This point is not relevant to the study used as the quantitative basis for risk assessment.
- *There are no chronic studies to relate serum levels and chronic effects relevant to humans. Subchronic studies are too short to achieve steady state, especially in rats.*
  Response: An uncertainty factor to account for effects that could occur from a longer exposure duration was applied. The effects observed in shorter term studies are effects that occur from exposures of short duration. The risk assessment is based on the serum level at the time that the effect was observed, and the exposure is reflected by the serum level, regardless of whether or not steady state has been achieved at that time.

Comment (2015): One commenter supported the choice of uncertainty factors used to develop the draft Interim Specific Ground Water Criterion, including the intraspecies uncertainty factor of 10, the interspecies uncertainty factor of 3 for toxicodynamic differences, the duration of exposure uncertainty factor of 10, and the uncertainty factor of 3 for an incomplete database. They stated that the choice of uncertainty factors was consistent with those commonly applied in other risk assessments based on non-carcinogenic endpoints.

Response: This comment is acknowledged.

Comments (2015): Two commenters disagreed with the use of an uncertainty factor of 3 for incomplete database. Both commenters stated that publication of the Das et al. (2015) study that was used as the basis for the quantitative risk assessment should reduce database uncertainty, and that there had been no other change in the relevant scientific literature that indicates a need for this uncertainty factor. One commenter suggested that the database uncertainty factor of 3 may have been added to offset the change in the relative source contribution factor that results in an increase in the health-based water value by a factor of 2.5.

*Response***:** The fact that the study of developmental effects of PFNA in mice, presented earlier in abstract/poster form by Lau et al. (2009), is now published in a peer reviewed paper by Das et al. (2015) is not relevant to the choice of uncertainty factors.

The Department has reviewed the DWQI Health Effects Subcommittee's evaluation of the choice of uncertainty factors for development of a health-based value for chronic exposure to PFNA in drinking water. The Subcommittee conducted an in-depth review of the application of the database uncertainty factor in previous EPA, DEP, and DWQI risk assessments. The Subcommittee concluded that an additional uncertainty factor of 3 is appropriate, is consistent with EPA guidance, and is consistent with its use in previous EPA, DWQI, and DEP risk assessments. The Department concurs with the Health Effects Subcommittee's conclusions on this issue.

The evaluations of uncertainty factors and the Relative Source Contribution factor were conducted separately without regard to the water concentration that would result. The rationale for the choice of Relative Source Contribution Factor is presented below.

Comment (2015): One commenter stated that an uncertainty factor of three to extrapolate from rodents to humans is overly conservative, because it is well established that rodent models are particularly sensitive to this class of compounds.

Response: An uncertainty factor of 3 to account for toxicodynamic differences between animals and humans is standard risk assessment practice.

This comment apparently refers to the greater sensitivity of rodents than humans to liver tumors that occur through activation of PPAR-alpha. As discussed in detail in the document, there is extensive evidence that the hepatic effects of long chain perfluorinated carboxylates, including PFNA and PFOA, also occur through non-PPAR alpha modes of action, for which human relevance is not in question. Two recent papers provide important additional information on this issue. In CD-1 mice exposed *in utero* to PFOA, hepatocellular hypertrophy at 3 and 13 weeks of age was accompanied by mitochondrial alterations in the liver cells, while there was no evidence of hepatic peroxisome proliferation, a marker of PPAR-alpha activation (Quist et al., 2014). A second study evaluated liver lesions at age 18 months in CD-1, wild type, and PPAR-alpha null (Knockout) mice with prenatal exposure to PFOA (Filgo et al., 2014). Liver carcinomas and/or adenomas did not occur in controls in any of the three mouse strains, but were found in PFOA-treated CD-1 and PPAR-alpha Knockout mice, but not Wild Type mice that are genetically identical to the Knockout mice with the exception of having functional PPAR-alpha receptors. Non-neoplastic hepatic effects (hepatocellular hypertrophy, bile duct hyperplasia, and hematopoietic cell proliferation) were more frequent and/or more severe in PPAR-alpha Knockout than wild type mice. Furthermore, the human relevance of non-hepatic effects that are mediated by PPAR-alpha, including developmental and immune effects, is not in question.

Comment (2015): One commenter stated that an uncertainty factor of 10 for duration of exposure is not justified and is not consistent with USEPA guidelines and that an uncertainty factor of 1 should be used. This comment is based on information presented in the USEPA Office of Water (2014) Draft Health Effects Document for Perfluorooctanoic Acid (PFOA). The commenter states the USEPA analysis indicates that serum levels of the closely related compound, PFOA, are similar for different exposure durations and Tardiff et al. (2009) uses the same value of 1 for the UFs based on the same rationale.

Response: The Department disagrees with the rationale for not including an uncertainty factor for duration of exposure that is presented in the USEPA Office of Water (2014) document cited. The Department reviewed and submitted comments on this draft document, including the following comment on this specific issue: "All of the studies listed in Table 5-14 are of subchronic duration including the 6 month monkey study (Thomford et al., 2001). The rationale for reducing the uncertainty factor for less than lifetime exposure from 10 to 1 for the HED PODs is not clear and does not appear to be supportable as described. The explanation given is that the HEDs reflect steady state serum values. However, this UF is intended to protect for additional or more severe effects than can occur from exposures of longer duration, not because steady state serum values have not been reached during the dosing period. This uncertainty factor is routinely applied in Reference Dose development without consideration of the time needed for

the chemical to reach steady state, including for RfDs for chemicals with very short half-lives for which steady state is reached quickly, long before dosing ends."

Additionally, the exposure duration for Das et al. (2015), the study used as the basis for quantitative risk assessment for PFNA, was only 17 days, and, as stated in the draft Technical Support Document: "No chronic toxicology studies of cancer or other effects that may occur after longer exposures and/or in old age have been conducted…. Results of the subchronic (Mertens et al., 2010) and the two-generation (Stump et al., 2008) suggest that additional and/or more severe effects may occur as exposure duration increases."
Comment (2015): One commenter combined the factor that relates the internal dose (serum level) in humans and animals from the same administered dose (mg/kg/day) with the total uncertainty factor of 1000, and stated that the total uncertainty factor is between 300,000 and 1 million and is excessive.

*Response***:** The calculation of the "uncertainty factor" presented by the commenter is not relevant to the derivation of the health criterion.

It is generally agreed upon that interspecies comparisons for perfluorinated compounds such as PFNA should be based on serum levels (a measure of internal dose) rather than administered dose. The internal dose is most relevant to toxicity because it reflects the dose reaching target tissues. Because of large interspecies pharmacokinetic differences, a given administered dose (mg/kg/day) results in a much higher internal dose (serum level) in humans than in experimental animals. Internal dose is the relevant measure in regard to toxicity, as it is relevant to the dose reaching target organ(s).

Because exposures to humans and animal species are compared on the basis of serum levels, the Point of Departure is based on serum concentrations and an uncertainty factor to account for interspecies kinetic differences is not used. Uncertainty factors are applied to this Point of Departure. The ratio of the internal doses in humans and experimental animals from the same administered dose is not an uncertainty factor. It is not appropriate to include it when calculating the total uncertainty factor used in the risk assessment.

Comment (2015): One commenter stated that the serum-based approach is appropriate, but that this approach should reduce the uncertainty factors.

Response: The default interspecies uncertainty factor of 10 is not used. This default uncertainty factor is composed of two equal components to account for pharmacokinetic and pharmacodynamics differences between species. Because exposures to humans and animal species are compared on the basis of serum levels, an uncertainty factor to account for interspecies kinetic differences is not used. The interspecies uncertainty factor of 3 is used to account for pharmacodynamics differences.

Focus Questions 3 and 4 (2015): Are you aware of additional data or technical information relevant to the choice of Relative Source Contribution factor? Is the Relative Source Contribution factor consistent with current USEPA guidance and the use of uncertainty factors in previous risk assessments developed by USEPA, NJDEP, and DWQI?

Comments (2014): Four commenters provided comments on the Relative Source Contribution (RSC) factor of 20% used in the 2014 draft document. Two commenters supported the use of a Relative Source Contribution of 20%, and one of these stated that a Relative Source Contribution factor of 20% is supported by Domingo (2012) who found that most PFC exposure in the general population comes from food. Two commenters stated that a Relative Source Contribution factor of 20% is too conservative. One of these commenters stated that because PFNA is no longer used to make PVDF, air exposure has been eliminated. Therefore almost all exposure is from drinking water and an 80% Relative Source Contribution factor should be used. The second commenter stated that more than 90% of PFC exposure in the general population is from the diet (Fromme et al., 2009) and that recreationally caught Delaware River fish consumption is likely to be low due to existing fish advisories. They suggested that a chemical-specific Relative Source Contribution factor be developed based on available data on non-drinking water exposure to PFNA, collection of additional data on pathway-specific exposures, and assumptions on relative contribution of drinking water in locations identified as having elevated levels of PFNA in drinking water. They further stated that a Relative Source Contribution factor of 20% is inconsistent with an NJDEP presentation on PFOA showing that 50% of exposure would come from drinking water at the current guidance value of 40 ng/L.

Response: A Relative Source Contribution factor of 20% was proposed in the 2014 draft document, in part, because of concerns about exposure to PFNA from consumption of recreationally caught fish. Elevated PFNA concentrations were found in fish from the Delaware River in 2004-2007. However, PFNA was not-detected in any of the more recent samples of the same species of fish from the same locations in 2010 and 2012. In regard to the two citations cited by the commenters indicating that diet is the main source of PFC exposure, it should be noted that these studies did not specifically focus on PFNA. Sources and uses of PFNA are very different than for other PFCs, and conclusions about sources of other PFCs such as PFOA and PFOS may not be applicable to PFNA. The fact that air emissions of PFNA have ceased does not indicate that almost all exposure now comes from drinking water and that the least stringent RSC recommended by USEPA (80%) should be used. In NHANES, PFNA is found ubiquitously in the blood serum of the U.S. general population, while drinking water contamination with PFNA occurs very rarely on a national basis. Exposures may arise from consumer products, diet, contaminated soil and dust, both from PFNA itself and from conversion of precursor compounds to PFNA in the environment and in the human body, and the magnitude of these non-drinking water exposures is reflected in the NHANES serum data. The conclusions presented by NJDEP about PFOA exposure from drinking water at the NJ guidance level compared to general population exposure are not relevant to PFNA since the PFOA guidance level and the general population exposure level to PFOA are different than the proposed PFNA interim ground water criterion and the general population exposure to PFNA.

Based on the considerations discussed above, the 95th percentile PFNA serum level from the most recent NHANES data (2011-12) is assumed to represent a reasonable and protective estimate of total non-drinking water exposure and is considered appropriate for use in developing a chemical-specific RSC for PFNA. This issue is further discussed in the response to comments received in 2015 (below).

Comments (2015): Three commenters submitted comments on the choice of Relative Source Contribution (RSC) factor. One commenter stated that an RSC based on the 95th percentile serum level from NHANES is not necessarily representative of exposures from non-drinking water sources in areas known to be contaminated with PFNA and recommended that the default RSC of 0.2 be used. This commenter disagreed with the conclusion that the most recent data in which PFNA was not detected in two species of fish from the Delaware River do not suggest elevated exposures to PFNA from recreationally caught fish. The commenter states that studies of PFCs in a variety of fish species suggest that it cannot be assumed that PFNA is not elevated in fish species other than the two species monitored in the Delaware River. The commenter also states that exposures through other media such as indoor air and locally grown food (such as through uptake into plants) could lead to elevated exposures in areas contaminated by PFNA.

Two commenters disagreed with use of an RSC based on the 95th percentile serum level from NHANES. Both of these commenters stated that use of the 95th percentile does not follow EPA guidance and that EPA recommends use of an average or median (50th percentile) value as the basis for the RSC. One of these commenters noted that the health-based drinking water value is very sensitive to the choice of the NHANES serum percentile used as the basis for the RSC.

Response: The first commenter states that the 95th percentile value for the U.S. general population is not sufficiently protective based on possibility that non-drinking water exposure to PFNA in localities affected by industrial contamination may exceed the 95th percentile for the general population. As discussed below, EPA generally recommends a mean value be used for the RSC. It should be noted that the 95th percentile for serum PFNA from NHANES (2011-12) is about 3-fold higher than the mean value. As above, elevated levels of PFNA were found in two species of fish (white perch and channel catfish) in the Delaware River near the presumed source of PFNA contamination in 2004-2007, suggesting that local residents could be exposed to PFNA through consumption of recreationally caught fish. However, PFNA was not detected in more recent monitoring of the same two species of fish in 2010-2012, a time period during which discharge of PFNA from the presumed source ceased. As noted by the commenter, PFNA levels in these two fish species may not necessarily be indicative of all recreationally consumed fish species, and the lack of data on other fish species is an uncertainty in the exposure assessment. However, we are not aware of any data suggesting that elevated exposure from fish consumption is currently occurring in this region. We are also unaware of any data on PFNA in crops or PFNA in indoor air in areas of New Jersey where drinking water is contaminated with PFNA. In regard to uptake into locally grown crops, it should be noted that several publications on experimental studies of PFC uptake into plants have shown that uptake decreases logarithmically as chain length increases, and that uptake of PFNA into plants is less than for PFOA and much less than for the shorter chain PFCs (Blaine et al., 2013, 2014; Yoo et al., 2011).

The other two commenters state that EPA guidance recommends using the mean, not an upper percentile value for the exposure basis for the RSC. The EPA (2000) guidance on choice of Relative Source Contribution factor was developed for use in deriving human health based ambient water quality criteria (i.e. surface water quality criteria) based on exposure through drinking water and/or fish consumption. While EPA develops **national** water quality criteria, states may adopt the national criteria or develop their own criteria. EPA (2000) recommends the use of a combination of central tendency and upper percentile values in its exposure assumptions

for national criteria. For the national criteria, a mean value for RSC is used in combination with upper percentile values for drinking water and fish consumption. When populations within a state could have higher exposures than the general U.S. population, EPA recommends that the state use alternate (e.g. more protective) assumptions. NHANES does not provide a geographical breakdown of its exposure data, and the mean NHANES serum concentration for the U.S. as a whole may not be representative of exposures in N.J. Non-drinking water exposures in N.J. may reflect multiple overlapping sources of PFNA including those background exposures that are influenced by air transport within N.J., and this may be particularly true in communities where groundwater has been impacted by past industrial use and discharge of PFNA. In contrast, mean national estimates of exposure, as indicated by the mean serum levels identified in NHANES, reflect exposures in large parts of the U.S. where there are few or no sources of PFNA manufacture or use.

Also relevant to this issue, the Maine Department of Health and Human Services (2014) developed a Health-based drinking water value for another biologically persistent PFC, PFOA, using an RSC based on the subtraction approach and using the 95th percentile NHANES serum data.

Based on the considerations discussed above, the Department concludes an RSC based on the 95th percentile of NHANES data is appropriate for use in development of the Interim Specific Ground Water Quality Criterion for PFNA.

Comment (2015): One commenter states that the RSC is presented as a fixed quantity, when in fact the contribution of the drinking water pathway should vary depending on the PFNA concentration in water.

Response: The commenter apparently did not understand that the RSC is applied to the target human serum level (analogous to a Reference Dose, but in terms of serum level) in the development of the Interim Specific Ground Water Quality Criterion. Using the subtraction method, the contribution to human serum from non-drinking water exposures is subtracted from the target human serum level to determine the contribution to serum level that may come from drinking water. The RSC is not relevant to the range of serum levels resulting from exposure to drinking water with varying levels of contamination.

Comment (2015): One commenter stated that the RSC is not consistent with current USEPA guidance because the exposure assumptions for drinking water consumption and body weight are not consistent with the most current EPA guidance. They recommended use of exposure factors from the EPA (2011) Exposure Factors Handbook and the OSWER (2014) Directive 9200.1-120.

Response: The EPA (2011) Exposure Factors Handbook recommends a mean value of 16 ml/kg/day for drinking water consumers of all ages, while USEPA (2004; Estimated Per Capita Water Ingestion and Body Weight in the US; EPA-822-R-00-001; Washington, DC.) recommended 17 ml/kg/day. The EPA (2011) value will be cited in the final document. In developing risk assessments based on chronic drinking water exposures, including Interim Specific Ground Water Criteria, NJDEP generally relies on exposure assumptions used by the

USEPA Office of Water in its drinking water risk assessment. Consistent with current practice of the EPA Office of Water, the default exposure factors used are 2 L/day drinking water consumption and 70 kg for adult body weight.

6. Additional comments

Comments (2014): One commenter stated that the draft criterion is consistent with the NJDEP published derivation for PFOA and with EPA's principles of Reference Dose development and drinking water exposure assessments, and that the use of available data and well-reasoned description of the derivation of the criteria was well noted. Three other commenters stated that the criterion derivation was generally well done, that the document includes a thorough review and fair evaluation of up to date health effects studies, and/or that the basis of the standard is fully documented.

Response: These comments are acknowledged.

Comment (2015): One commenter summarized the approach used for the risk assessment and stated that they concur with this approach.

*Response***:** This comment is acknowledged.

Comment (2014): One commenter stated that no guidance values or standards have been developed by USEPA or other states, and that the reason for this is a lack of suitable information to support risk assessment of PFNA.

Response: It is acknowledged that the Department is not aware of any guidance values or standards for PFNA that have been developed by USEPA or other states. However, the primary reason for this is not a lack of necessary data, but because drinking water contamination by PFNA has not been found in locations other than NJ. There is a need for NJ to develop a ground water criterion for PFNA to address this NJ-specific situation.

Comments (2014 and 2015): One commenter stated that there are insufficient data to demonstrate that PFNA may cause human health risk. Another stated that currently available epidemiological evidence is insufficient to establish any adverse human health effect caused by PFNA exposure. One commenter stated that there is no scientific evidence of human health impacts from exposure to trace levels of PFNA in New Jersey or elsewhere.

Response: As stated by the commenter, the Draft Health-Based MCL Support Document for PFNA acknowledges the limitations of the epidemiologic evidence and states that human epidemiology data is not used as the basis for the risk assessment. It should be noted that this also is the case for most environmental contaminants for which human health risk assessments and drinking water standards have been developed by USEPA, DEP, and DWQI.

Comment (2015): One commenter stated that the available scientific evidence is insufficient to characterize PFNA toxicity, and that the methods used to overcome the gaps in the scientific knowledge are not technically supportable and lead to extreme overestimates of potential toxicity. They also stated that available data, when comprehensively assessed, do not indicate that PFNA causes toxicity in people. They stated that it is premature to develop a maximum a

health-based standard for PFNA.

Response: As discussed in the Technical Support document, there is a considerable database on effects of PFNA in animals and humans. The data demonstrate that PFNA causes several types of toxicity in experimental animals and has been associated with health endpoints in humans. These data are sufficient to develop an Interim Specific Ground Water Quality Criterion for PFNA. The database for PFNA is at least as complete as for many other contaminants for which health-based ground water or drinking water standards have been developed, and they are sufficient to develop an interim specific ground water criterion for PFNA.

Comment (2014): One commenter stated the literature review strategy was not provided, that there was no systematic review of the literature while USEPA used systematic review in its recent PFOA and PFOS documents, and that the process for evaluating data quality was not provided. The commenter also cited USEPA data quality guidance and stated that they were not followed.

Response: The statement that the USEPA Office of Water used systematic review in its recent draft PFOA and PFOS documents is incorrect. Additionally, no officially accepted guidance from USEPA or other agencies regarding systematic review in human health risk assessment has been developed.

For the draft document, PubMed and other relevant databases were searched for information on PFNA. Additional relevant citations from the studies located in the literature search were obtained. A primary purpose of the public comment process was to obtain any additional relevant data that were not located previously. As discussed in the draft document, additional information about the Surflon S-111 studies (Stump et al., 2008; Mertens et al., 2010) was requested from the study sponsors but was not provided. Also, additional unpublished studies of PFNA/Surflon S-111 conducted by the study sponsor, including a study that was cited in Mundt et al. (2007), were requested but not provided.

The three USEPA data quality guidance documents that were cited are not intended to be applied to the development of human health risk assessments. The scientific integrity, completeness, relevance and utility of each study was evaluated on the basis of professional judgment and the description of each study in the text allows the reader to assess that judgment.

Comment (2014): One commenter stated that a Lowest Observed Adverse Effect Level (LOAEL) instead of a No Observed Adverse Effect Level (NOAEL) was used as the basis for the risk assessment.

Response: The Point of Departure (POD) for the risk assessment was not a Lowest Observed Adverse Effect Level (LOAEL) but rather a BMDL, the lower confidence limit of the Benchmark Dose, which is the lower 95% confidence bound on the dose corresponding to the lowest response that is consistent with the observed data. The BMDL is considered to be an estimate of the No Observed Adverse Effect Level (NOAEL), but is based on the entire dose-response curve for the endpoint of interest, rather than just the fixed doses administered in the study.

Comment (2014): A commenter stated that the dose-response was based on serum levels measured on the last day of dosing, that effects could have resulted from lower exposures earlier, and thus that risk may be underestimated.

Response: It is acknowledged that the average serum level during the dosing period would be lower than the serum level on the last day of dosing. Without detailed data on the time course of the relationship of the serum levels to the effect over time, it is most defensible to base the risk assessment on the serum level measured at the end of dosing, the same time point at which the effect was assessed.

Comment (2014): One commenter stated that there was no effort to use dose-response data based on administered dose from Wolf et al. (2010).

Response: It is generally accepted that risk assessments for persistent PFCs such as PFNA must be made on the basis of internal dose (serum level), not administered dose (Post et al., 2009; Tardiff et al., 2009; USEPA, 2014), because a given administered dose results in very different internal doses in humans and experimental animals. Specifically, in Wolf et al. (2010), it is clearly evident from the data that the same administered dose resulted in different serum levels in WT and knock out mice, particularly in the mice that had given birth. A dose-response assessment based on administered dose would not consider these important differences in internal exposure.

Comment (2014): One commenter stated that the ingestion rate and body weight (weighted) for a child age 1-6 should be used.

Response: Risk assessments for chronic exposure to drinking water are usually based on lifetime exposures. The uncertainty factor of 10 for intra-individual human variation is intended to protect sensitive human subpopulations including children. The draft criterion was based on the average daily water consumption value recommended by USEPA (2004) of 0.017 L/kg/day.

Comment (2015): One commenter suggested that the ISGWQC be based on the default Relative Source Contribution factor of 0.2 and exposure factors based on the higher drinking water consumption rate on a body weight basis of children age 1-6. They developed an Interim Specific Ground Water Quality Criteria values based on median and 90th percentile drinking water consumption values for a child age 1-6 of 5 ng/L (median exposure) and 3 ng/L (90th percentile exposure), and propose a value of 5 ng/L at a minimum.

Response: For reasons discussed above, it was concluded that it is appropriate to use a higher chemical specific RSC, rather than the default RSC of 0.2, for PFNA. Additionally, if higher drinking water consumption during childhood were to be considered, a time weighted average of exposures during childhood and adulthood would be used to develop a chronic value, rather than exposure during childhood (age 1-6) alone. As discussed above, the PFNA risk assessment utilizes an estimated 200:1 serum to drinking water ratio, and the approach proposed by the commenter would entail additional manipulations of this ratio, introducing additional uncertainty into the exposure evaluation. Furthermore, the drinking water concentration resulting from the time weighted average values presented by the commenter for age 1-6 (3 ng/L) and ages 6-70 (5

ng/L) (based on an assumed lifetime of 70 years) is only 8% lower than if the lower value for ages 1-6 was not considered.

Comment (2014): One commenter stated that no rationale was given for rounding the value of the criterion from 17 ng/L to 20 ng/L.

Response: Ground water quality criteria are rounded to one significant figure as per N.J.A.C. 7:9C-1.7 c 4.

Comment (2014): One commenter stated that cumulative risks of PFC mixtures should be considered.

Response: The possibility that exposures to other PFCs along with PFNA may result in cumulative risks is acknowledged and is discussed as an uncertainty in the draft document.

In addition, Section 12 d of the Brownfield and Contaminated Sites Act (N.J.S.A. 58:10B) gives the Department the authority to establish soil and ground water remediation standards: "d. The department shall develop minimum remediation standards for soil, groundwater, and surface water intended to be protective of public health and safety taking into account the provisions of this section." However section 12d of the statue further states: "The health risk standards established in this subsection are for any particular contaminant and not for the cumulative effects of more than one contaminant at a site." As such, the Department is precluded by statute from developing remediation standards based on the cumulative risks of PFC mixtures.

Comment (2014): Inhalation and dermal exposures during showering and bathing may be of concern and should be evaluated.

Response: As discussed in the draft document, inhalation exposure to PFNA is not considered to be of concern because PFNA is not volatile in the ionized form present in drinking water. The potential for dermal exposure has been evaluated and is not considered to be of concern, since it was estimated to be several orders of magnitude less than ingestion exposure based on conservative assumptions (NJDOH, 2014). This information on dermal exposure has been added to the revised document. Exposure through incidental ingestion during bathing has also been evaluated, and it was determined that this pathway is not of concern at the proposed Interim Ground Water Quality Criterion of 20 ng/L.

Comment (2014): One commenter asked why serum data are required for the derivation of the PFNA criterion but not for the toxicity study used as basis for the NJ criterion for PFOA.

Response: NJ developed a drinking water guidance value, not a ground water criterion, for PFOA. The drinking water guidance value is based on measured or modeled serum levels from the animal studies identified by USEPA (2005) in their draft risk assessment for PFOA as the No Observed Adverse Effect Level (NOAELs) or Lowest Observed Adverse Effect Level (LOAELs) for non-carcinogenic endpoints.

Comment (2014): One commenter stated that there are insufficient data to develop multipliers for relative potency of PFCs based on similar structures, and that there are insufficient data to support estimates of relative potency of PFNA based on data for PFOA.

Response: The "toxicological potency" (e.g. Reference Dose) for PFNA is based on data from studies of PFNA, not PFOA or other PFCs. A multiplier for relative potency of PFNA based on PFOA or other PFCs was not developed.

Comment (2014): One commenter stated that the cross-sectional epidemiology data for PFCs are consistent across several types of studies, and are supported by associated gene expression changes (for cholesterol), strongly suggesting causality. The commenter suggested that the incidence rates from cross-sectional studies could be used as the basis for risk assessment. Another commenter stated that they agree with the statement in the draft document that the epidemiology data do not prove that PFNA causes any human health effect, and that it is not appropriate to assume that associations of health effects with PFOA in drinking water are relevant to PFNA.

Response: The epidemiology data are considered as part of the overall weight of evidence for the potential human health effects of PFNA. While the epidemiology data suggest that PFNA may cause human health effects at the exposures prevalent in the general population, causality cannot be proven from these data. Therefore, it is not appropriate to use these data as the basis for the quantitative risk assessment. It should be noted that the gene changes associated with cholesterol were part of a study of the related compound, PFOA, not PFNA. As discussed in the draft document, available data indicate that the toxicity of PFNA is similar to PFOA, but that it is more potent and more biologically persistent; this conclusion has been stated in a several published studies of PFNA. Data for PFOA are considered relevant as supporting information in the weight of evidence evaluation for PFNA but is not used as the basis for the PFNA risk assessment.

Comment (2014): A commenter stated that there is no critical analysis of the epidemiology studies and that there is insufficient information on design, methods, potential confounders and biases, control of confounders, participation rates, and statistical approaches.

Response: The design, results, strengths and limitations of each of the epidemiology studies are discussed at an appropriate level of detail in the draft document.

Comment (2014): One commenter stated that a systematic evaluation of the weight of evidence of epidemiology data show that the observed associations are not strong and can reasonably be explained by bias, confounding, or chance, that the epidemiology results are not consistent across studies, that it is not known if exposure preceded effects, that a positive dose-response was not observed for most effects, that a biologically plausible mechanism for the effects has not been established, and that the human and animal results are not coherent. Additionally, they stated that the weight of evidence for the epidemiology data were not synthesized using standard guidelines, such as the Bradford Hill criteria, to conclude that the evidence is insufficient to show that PFNA causes any adverse human health effect. They suggested that, if it has been decided not to conduct a formal weight of evidence evaluation, the reasons should have been stated.

Response: Because the epidemiology data are not used as the basis for the quantitative risk assessment, an overall weight of evidence evaluation for these data was not conducted. This information has been added to the revised document.

Comment (2014): A commenter stated that there was an excessive focus on positive studies versus negative and null studies and that negative findings for some health endpoints are not mentioned, implying that associations are established when they are not. Specific examples mentioned included studies of cholesterol, glucose metabolism/diabetes, vaccine response, thyroid parameters, and behavioral effects in children. They also stated that the Summary highlights unreplicated positive results.

Response: The positive and negative findings in the epidemiology studies are discussed with an appropriate level of detail in the draft document. As above, the results of the diabetes studies in adolescents have been clarified in the revised document. The Summary was posted prior to the Draft Technical Support Document (TSD), is not part of the TSD, and is not an intended subject of the request for comments.

Comment (2014): One commenter questioned the validity of exposure classification based on serum PFNA at a single time point.

Response: Since PFNA has a human half-life of several years, serum levels represent overall long term exposures and do not fluctuate rapidly. Therefore, it is appropriate to use a single serum measurement as an indicator of long term exposure.

Comment (2014): Six studies identified as prospective birth cohort studies, which reduce chance of reverse causality, are not identified as such, and are incorrectly stated to be cross-sectional.

Response: Of the six studies noted by the commenter, five are prospective cohort studies and one is a nested case-control study design. The document has been revised to correctly note the study design or to make the study design employed in these studies more clear.

Comment (2014): One commenter stated that analogies between immune and metabolic effects in humans and animals are superficial, inappropriate, highly selective, and tenuous, and that the endpoints discussed are not comparable between humans and animals.

Response: The statement in the draft document were not intended to make specific analogies between the immune and metabolic effects in animal studies and the associations found in humans, but rather to note that studies in both animals and humans found effects related to metabolism and immune function. These statements have been clarified in the revised document.

Comment (2015): Two commenters stated the Benchmark Dose is based on unpublished data from the study reported in Das et al. (2015), and that personal communications were cited in the DWQI Health Effects Subcommittee document (upon which Interim Specific Ground Water Quality Criterion relies, according to the commenter).

Response: The PFNA Benchmark Dose is not based on unpublished data. It is based on data

on PFNA serum levels and liver weight on GD 17 in pregnant mice from a peer-reviewed scientific journal article (i.e., Das et al.; 2015). As is common practice in scientific publications, Das et al. (2015) present much of their results in figures and graphs, rather than in tables of numerical data. The numerical data for liver weight and PFNA serum concentrations in the pregnant mice on GD 17 were obtained from C. Lau. As discussed above, the individual animal data used to generate the summary statistics for liver weight and PFNA serum concentrations were also provided by the investigator. The Office of Science independently verified the summary statistics used for BMD modeling from the individual animal data.

The personal communications cited in the DWQI document provided supplementary information about details that were not included in the published paper. While this information was included because it is of interest, it does not impact the conclusions presented in the DWQI document.

Comment (2015): One commenter stated that the risk assessment approach based on comparing serum levels in experimental animals and humans should be reconsidered, since many other studies might potentially be considered as the basis for Benchmark Dose modeling.

Response: A risk assessment approach based on administered dose that does not account for the large pharmacokinetic differences between humans and laboratory animal species is not appropriate for biologically persistent PFCs such as PFNA. There are several studies (Mertens et al., 2010; Stump et al., 2008; possibly others) for which PFNA serum data were collected but these data were not provided by the study sponsors when requested. If the serum data from these other studies were provided, BMD modeling could be conducted for the endpoints evaluated in these studies.

Comment (2015): One commenter provided comments and criticisms of the BMD estimates based on administered dose presented by Das et al. (2015).

Response: The BMD estimates presented in Das et al. (2015) are based on administered doses, not serum levels, and are not relevant to the BMD modeling used as the basis for the IGWQC.

Comment (2015): One commenter submitted a report containing data on PFNA serum levels from 25 Paulsboro residents and one resident of another nearby community whose private well is contaminated with PFNA. These serum data were reported to have been collected by attorneys representing residents in a lawsuit related to exposure to PFNA in drinking water against the company that is the presumed source. The report also presents historical well usage data and PFC monitoring data for the Paulsboro public water system. Through the use of assumptions about the toxicokinetics of PFNA in humans, the report estimates serum to drinking water ratios for Paulsboro residents and concludes that the 200:1 serum to drinking water ratio used as the basis for the IGWQC is several fold too high.

Response: In a separate submittal on legal and procedural issues from the attorneys representing the presumed source, they state that they obtained these data from the attorneys representing the residents. It is not appropriate for the Department to consider these serum data or the analysis based on them because they were not obtained as part of a scientific study. The collection of these serum samples and the reporting of information related to the subjects and

the serum samples did not involve scientists, a protocol or study design, or other components of a valid scientific study.

Citizen Concerns (2014):
Comments were received from a resident of a community where PFNA was found in a public water supply well. The commenter asked what has been done to correct the contamination, if home filters that will remove PFNA are available, whether the water is safe for children (age 10 and 14), and why must residents pay for unsafe water. The commenter requested that bottled water be provided until the situation is resolved.

Response: In January 2014 as a result of testing of the drinking water for PFCs, West Deptford stopped using Well #3 as a precaution. The Department had requested that the New Jersey Drinking Water Quality Institute develop a drinking water standard for PFNA, and the Drinking Water Quality Institute has recommended a drinking water standard of 0.013 parts per billion (micrograms per liter).

An investigation is currently underway by Solvay to identify public and domestic wells that are impacted by PFNA. In 2010, Solvay installed and began operation of a pump and treat system, to control the migration of pollutants in groundwater on their site. Offsite contamination still requires delineation and remediation. A critical step in remediation is to establish an Interim Groundwater Quality Criterion to regulate the discharge of this pollutant in groundwater. Further delineation of the contamination, a clear understanding of the fate and transport of the pollutants, and criterion are required before all final remediation plan(s) can be put in place. The commenter is referred to the New Jersey Department of Health website for information regarding the treatment of perfluorinated chemicals in home drinking water and concerns regarding children at http://www.state.nj.us/health/eohs/pfc_in_drinkingwater.shtml

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