Response to Public Input on Draft Interim Ground Water Quality Criteria and Draft Interim Practical Quantitation Levels for Eleven Chemicals

The New Jersey Department of Environmental Protection (Department) has developed and requested public input for draft Interim Ground Water Quality Criteria and analytical draft interim practical quantitation levels (PQLs) for 11 chemicals (Table 1). The Department published these proposed values and their technical basis to solicit public input in the interest of transparency and obtaining additional relevant information. The basis for the draft interim criteria for these chemicals was developed over the past several years, while the draft PQLs were developed more recently. The Department was particularly interested in any new toxicity data or information relevant to the derivation of the draft interim criteria.

The Department received comments on 7 of the 11 chemicals. No comments or information was received for tri-ortho-cresyl phosphate, tri-cresyl phosphate (mixed isomers), 1-chloro-1,1-difluoroethane or 1,1,2-trichloro-1,2,2-trifluoroethane. Comments were received from the following stakeholders:

- Arcadis U.S.
- Chemical Council of NJ
- Department of Defense
- Dow Chemical
- ERM
- Eurofins Environment Testing US
- Spectrum Analytical, Inc.
- HDR, Inc.

Table 1. Draft Interim Specific and Generic Ground Water Quality Criteria and Draft Interim PQLs

Parameter	Draft Interim Criterion	Specific or Generic	Draft Interim PQL
1,2,4-Trimethylbenzene	100 ppb	Generic (non-carcinogen)	0.08 ppb
1,4-Dioxane[1]	0.4 ppb	Specific	0.1 ppb
1-Methylnaphthalene	5 ppb	Generic (carcinogen)	0.7 ppb
Cresols (mixed isomers)	50 ppb	Specific	0.1 ppb
Tri-ortho-cresyl phosphate	3 ppb	Specific	0.1 ppb

[1] The proposed draft interim specific ground water quality criterion and proposed interim PQL for 1,4-Dioxane are revisions to the existing interim specific ground water quality criterion and PQL established by the Department on 2/11/08 (http://www.state.nj.us/dep/wms/bwqsa/gwqs_interim_criteria_table.htm).

Tri-cresyl phosphate (mixed isomers)	3 ppb	Specific	0.1 ppb
1,1,1-Trifluoroethane	5 ppm	Specific	0.06 ppm
1-Chloro-1,1-Difluoroethane	100 ppm	Specific	0.5 ppm
1,1,2-Trichloro-1,2,2-trifluoroethane (Freon 113)	20 ppm	Specific	0.3 ppb
1,1-Dichloro-1-fluoroethane	500 ppb	Specific	30 ppb
Strontium	1,500 ppb	Specific	5 ppb

Summary of Comments and Responses for the Draft Interim Practical Quantitation Limits

Question 1: Are you aware of additional data or technical information concerning analytical methods to detect the chemicals listed that would affect the selected draft Interim practical quantitation limits (PQLs), especially 1,4-dioxane where the analytical sensitivity is not capable of quantification at or below the interim ground water criterion concentration?

Comment: One commenter did provide PQL comments for 1,4-dioxane but did not provide any new performance data to include in the analysis.

Response: No response is necessary

Comment: Several Commenters did provide performance data for the parameter 1,4 dioxane. The utilization of this data is presented in the response below.

Response: USEPA Method 522 performance information was provided by one commenter on June 1, 2015 from NELAP certified laboratories. Two of the four laboratories indicated that they could achieve the reporting limit (0.07 ppb and 0.04 ppb), at or below the recommended PQL value of 0.1 ppb. In addition, one commenter provided a reporting limit for 1,4-dioxane of 0.1 ppb by Method 8270 selective ion monitoring from their laboratory.

The Office of Science pooled the provided data to evaluate this information. The MDL information was combined with the values used to determine the PQL using the Department's traditional approach and a bootstrap estimate of the mean and upper confidence level determination was made for comparison of the USEPA methodology. The results of this statistical approach yielded an interlaboratory MDL upper confidence limit (UCL) of 0.06 ppb. The two laboratories that could not achieve the reporting limit exceeded the UCL of 0.06 ppb for the MDL and a decision was made to exclude these values from consideration.

Question 2: Are you aware of additional data or technical information concerning analytical methods to detect the chemicals listed that would affect the selected draft Interim practical quantitation limits (PQLs), especially 1,2,4-trimethylbenzene where the analytical sensitivity is not capable of quantification at or below the interim ground water criterion concentration?

Comment: One commenter provided guidance, state code, and QA requirement values from Ohio, Pennsylvania, and USEPA Region 9 that were above the recommended PQL value of 0.08 ppb for 1,2,4-trimethylbenzene.

Response: The Office of Science is tasked with assessing analytical capability to support the NJDEP Office of Ground Water Pollution Abatement by determining the latest state-of-the-art published capability to support the development of remediation levels that are chemical specific. Although all of the values presented by the commenter are below the IGGWQC 100 ppb level, the most sensitive published method was selected to enable the development of cleanup standards and site conceptual models. Although the calculated PQL is below the IGGWQC and is not the driver for this parameter, the Department still assesses the low level analytical capability.

Comment: One commenter provided selective ion monitoring quantification information for all of the stage one parameters (1,2,4-trimethylbenzene, 1,4-dioxane and 1-methylnaphthalene) from their laboratory which met or exceeded the sensitivity requirements for the recommended PQLs. They do not routinely determine 1,2,4-trimethylbenzene by USEPA Method 524.3, but utilize Method 6200 which is a 25 ml trap and purge technique. Their reporting limit for 1,2,4-trimethylbenzene is 0.5 ppb which is below the IGGWQC 100 ppb level.

Response: We appreciate the additional information that the commenter provided.

Question 3: Are you aware of additional data or technical information concerning analytical methods to detect the chemicals listed that would affect the selected draft Interim practical quantitation limits (PQLs), especially Tri-cresyl phosphate (mixed isomers) where the analytical sensitivity is not capable of quantification at or below the interim ground water criterion concentration?

Comment: One commenter provided a reporting limit for their laboratory of 1 ppb for cresols which is below the IGGWQC 50 ppb level. They do not routinely determine this parameter by USEPA Method 524.3, and did not provide a method reference in the comments.

Response: We appreciate the additional information that the commenter provided

Question 4: Are you aware of additional data or technical information concerning analytical methods to detect the chemicals listed that would affect the selected draft Interim practical quantitation limits (PQLs), especially 1-methylnaphthalene where the analytical sensitivity is not capable of quantification at or below the interim ground water criterion concentration?

Comment: One commenter provided selective ion monitoring quantification information for all of the stage one parameters from their laboratory which met or exceeded the sensitivity requirements for the recommended PQLs for 1-methylnaphthalene.

Response: We appreciate the additional information that the commenter provided.

Strontium:

Comment: A commenter stated that, in their laboratory, the current reporting level is 10 ppb via 200.7. The limit of detection for strontium by Method 200.7 is 10 ppb. Concentrating the sample will meet the Draft Interim PQL of 5 ppb. However, they cannot meet the Draft Interim Specific Ground Water Quality criterion of 1.5 ppb via Method 200.7, and they do not currently analyze Sr by Method 200.8.

Response: The PQL of 5 ppb was calculated using the procedure specified in the Ground Water Quality Standards and confirmed by the State primacy laboratory which has a reporting limit of 5 ppb. The comment submitted was in error stating that the Draft Interim Specific Ground Water Quality criterion of 1.5 ppb cannot be met by USEPA Method 200.7. The Draft Interim Specific Ground Water Quality criterion is 1500 ppb.

Summary of Comments and Responses for the IGWQS for 1-Methylnaphthalene (1-MN)

Comment: NJDEP applied a generic ground water criterion for chemicals with evidence of carcinogenicity because the cumulative uncertainty adjustments exceeded the limit of 10,000 for derivation of a chemical specific Reference Dose. Jin et al., (2012) provides sufficient information to develop a toxicity criterion for 1MN. The dose-response from this study should be modeled using benchmark dose analysis, thereby, eliminating the LOAEL-NOAEL uncertainty adjustment.

Response: We have re-examined the data from the Jin et al. (2012) study with respect to their suitability for benchmark dose analysis. There are several significant problems with applying benchmark dose analysis to these data. Several of the dose-response models available for continuous data in the USEPA's most recent version (2.6) of its BMDS software are over-parameterized for this data set containing only two doses (plus control). For organ weight data that are the most toxicologically significant endpoints, male spleen relative organ weight has a plateaued response at the highest dose, effectively resulting in a benchmark dose analysis driven by a single observation. Male heart relative organ weight is not adequately fit by any of the available models. Plateau response at the highest dose is also the case for the single cell liver necrosis endpoint suggested by the commenter, and for serum calcium concentration (an endpoint of uncertain significance), and basophil counts in females. The only endpoints for which there is adequate fit by any of the available BMDS models are segmented neutrophils and serum AST in males. The observed moderate change in these endpoints is of uncertain toxicological significance. For these endpoints, the available dose response models in the BMDS software give BMDL values that differ little from the lowest dose. Thus, while the lowest dose is a LOAEL for several endpoints, most notably organ weights, benchmark dose analysis is either not valid or not informative for these endpoints.

Comment: The effects seen at the lower of the two doses in the Jin et al. (2012) study should not be considered adverse and therefore, the low dose should be considered a NOAEL rather than a LOAEL.

Response: The Jin et al (2012) study showed adverse effects, most notably, changes in organ weights at the lower of the two doses. At the lowest dose, the relative and absolute decrease in spleen weight in males was 22%. This is supported by adverse effects in the Murata et al. (1993) study (albeit complicated by methodological problems) and the Rasmussen et al. (1986) study. Murata et al. (1993) reported significant changes in relative organ weight, including decreases in heart and increases in brain. In both of these studies, adverse effects were noted at doses below the lowest dose in the Jin et al. study. These studies support the identification of the lowest dose in Jin et al. as a LOAEL. In addition, the subchronic duration of the Jin et al. supports a broader interpretation of the potential implication of low-level adverse effects than might be applied in the context of a chronic study.

Comment: The weight of the toxicology data available for 1MN does not support a classification of 1-MN as carcinogenic.

Response: The Murata et al. (1997) study showed clear evidence of lung tumors in mice exposed to 1-MN. There was a potential for cross-contamination by 2-MN. However, as discussed in the draft document, the greater tumor incidence (and non-tumor toxicity) observed by Murata et al. for 1-MN compared to 2-MN suggests that 1-MN had a carcinogenic effect in these mice independent of a possible contribution from 2-MN. In addition, there is some additional support for a carcinogenic potential for 1-MN from *in vitro* genotoxicity/mutagenicity studies. While the draft document acknowledges that the quality of the database supporting a determination of carcinogenic potential is poor, the available evidence is compatible with the designation of "Suggestive Evidence of Carcinogenic Potential" under the USEPA's 2005 Guidelines for Cancer Risk Assessment. This designation does not require unequivocal evidence of human carcinogenicity.

Substantive Changes to the Draft Document

In reviewing the draft Interim Groundwater Criterion document for 1-MN in conjunction with the consideration of the external comments, the need for several relatively minor corrections and clarifications were recognized. The following summarizes those changes that are substantive (as opposed to strictly editorial). **However, it should be noted that none of these changes alters the interpretation of the key studies considered in the previous draft, nor do any of these changes alter the conclusions or the quantitative findings of the assessment**

1. In the discussion of the Jin et al. (2012) study, PCNA analysis was incorrectly characterized as a measure of DNA repair. It is, more correctly a measure of cell replication. This was corrected in the text. It is now additionally noted that lack of increased PCNA argues against a

proliferative response to 1-MN exposure that could potentially result in an increased mutation rate or clonal expansion of mutated loci.

2. In the draft document, doses in the Rasmussen et al. (1986) study were incorrectly reported as nmoles/kg and µg/kg. The correct units should be mmoles/kg and mg/kg. Thus, the correct doses should be 71, 142, and 427 mg/kg. This correction does not change the calculation of the Reference Dose.

3. In summarizing that data relating to mutagenicity and genotoxicity of 1-MN, the text was changed from stating that the high-dose mutagenic response may not be distinguishable from toxicity, to stating that high-dose mutagenicity may be secondary to toxicity.

4. In the Development of a Reference Dose section, the Human Equivalent Intake is amended to 1210 mg/day from 1209 mg/day due to a rounding error and the Human Equivalent Dose, derived from the Human Equivalent Intake is similarly amended to 17.29 mg/kg/day from 17.28 mg/kg/day.

Summary of Comments and Responses for the IGWQS for 1,2,4-Trimethylbenzene (1,2,4-TMB)

Question 1: Do you agree that there is insufficient information to develop an interim specific criterion for these constituents? If not, what information are you able to provide to allow the development of an interim specific criterion for these constituents?

Comment: NJDEP did not consider information that became available after March 2013, the date of the draft IGGWQC. The basis for the draft IGGWQS for 1,2,4-TMB basis drafted in 2013 does not consider the May 2015 USEPA SAB recommendations, including the SAB critique of the USEPA physiologically based pharmacokinetic (PBPK) modeling effort, and other additional information available both before and after the March 2013 recommendation of an IGGWQS. The May 2015 draft USEPA Science Advisory Board review of the August 2013 draft IRIS risk assessment indicates that there is enough information to develop a chemical-specific ground water criterion instead of relying on a generic criterion. Additional information, including post-2013 scientific literature and scientific literature related to C-9 aromatic hydrocarbons, should be reviewed before the proposal of the IGGWQC for 1,2,4-TMB. An IGGWQC should not be finalized prior to the completion of the IRIS assessment.

Response: NJDEP is aware of the 2013 USEPA IRIS draft assessment of 1,2,4-TMB and 2015 draft USEPA Science Advisory Board (SAB) review of the draft risk assessment. NJDEP agrees with the commenter that there are new data that weren't considered in its previous assessment. Since the USEPA IRIS Program has considered this newer material in its 2013 draft and is

currently in the process of reviewing its SAB's comments on that draft, NJDEP believes that it would be both appropriate and a wise use of resources not to undertake an independent review of the newer data pending its review of the anticipated USEPA final IRIS assessment. However, because there is a need for a New Jersey ground water criterion for 1,2,4-TMB at this time, an Interim Generic Ground Water Quality Criterion will be used. If additional relevant information, such as a final EPA IRIS assessment, becomes available, the IGGWQS will be reviewed to determine if a revision is warranted.

Comment: If default exposure assumptions for development of ground water criteria are used, the Reference Dose in the 2013 EPA IRIS draft would result in a ground water criterion for 1,2,4-TMB of 140 µg/L, which is higher than the proposed IGGWQC of 100 µg/L. Some of the comments from SAB 2015 review suggest a higher RfD might be derived. As a whole, nothing in the 2014-2015 SAB process suggests the RfD would go any lower than 140 µg/L, suggesting the generic proposed draft GWQC of 100 µg/L for 1,2,4-TMB is too conservative when the TMB body of science is considered.

Response: The Ground Water Quality Standards regulations specify that Ground Water Quality Standards, including those that are interim, are rounded to one significant figure. Therefore, the value of 140 µg/L mentioned in the comment would round to 100 µg/L, the proposed IGGWQC. However, the final USEPA IRIS Reference Dose could be higher or lower than the value presented in the 2013 draft document due to the USEPA's anticipated consideration of the recommendations of the SAB which include additional evaluation of the physiologically-based pharmacokinetic (PBPK) modeling, consideration of potential changes in application of uncertainty factors, and other recommendations.

Comment: Including toxicity information for C9 aromatic hydrocarbon and other TMB isomers in the evaluation of toxicity for 1,2,4-TMB has been used by other agencies and states. The commenter presented a discussion of information on C9 aromatic hydrocarbons and a summary of the evaluations of several other states and agencies that considered this information.

Response: As discussed above, NJDEP believes that given the status of the USEPA's newer assessment, it is not appropriate to develop a specific ground water criterion until USEPA has finalized its assessment. Because there is a need for a New Jersey ground water criterion for 1,2,4-TMB at this time, an Interim Generic Ground Water Quality Criterion will be used. If additional relevant information, such as a final EPA IRIS assessment, becomes available, the IGGWQS will be reviewed to determine if a revision is warranted.

Question 2: Do you agree with the classification as a carcinogen or non-carcinogen for the purposes of interim generic criterion development? If not, why not?

Comment: The commenter agrees with the NJDEP that the weight of the toxicology data available for 1,2,4 TMB do not support its classification as carcinogenic, and stated that this classification is also supported by the SAB 2015 report.

Response: NJDEP agrees with this comment.

Summary of Comments and Responses for the Draft ISGWQS for 1,1,1-Trifluoroethane (HCFC-143a)

Comment: Route-to-route extrapolation without accounting for the unstudied potentially less toxic nature of HCFC-143a via the oral exposure route may not be appropriate. Consideration should be given to including a modifying factor in the derivation of the oral NOAEL that, with appropriate justification, could raise the oral NOAEL to be higher than 7,000 mg/kg-day given that no oral absorption data are available for HCFC-143a and absorption efficiency via the oral and inhalation routes is not likely to be identical, especially given that the physical form of HCFC-143a is a gas.

Response: HCFC-143a is not highly reactive, and has limited aqueous solubility. It is, therefore, not expected to have point-of-contact toxicity in the respiratory tract, or specific respiratory tract toxicity. Rather, as discussed in the draft document, it is well absorbed and distributes systemically. Given these considerations, it is expected that the toxicity HCFC-143a will not be substantially influenced by the route of exposure. The underlying assumption in the commenter's suggestion of an upward adjustment to the oral NOAEL derived from the inhalation NOAEL is that HCFC-143a is likely to be less toxic by the oral route of exposure than by the inhalation route. The commenter, however, provides no scientific rationale to support this suggestion and we are unaware of any evidence to support such an assumption.

Comment: No justification is provided for the Office of Science's use of the maximum uncertainty factors of 10 for interspecies variability, intraspecies variability, subchronic-to-chronic extrapolation, and database insufficiency. With a derived oral NOAEL of 7,000 mg/kg-day, HCFC-143a has low potential toxicity. Because of the robust nature of the acute and subchronic inhalation studies described in the document, justification can be made that the subchronic-to-chronic uncertainty factor of ten (10) may be overly conservative and an uncertainty factor of three (3) may be more appropriate, especially since HCFC-143a was shown in animal experiments to cause no adverse effects at very high airborne concentrations in the subchronic study used as the basis for the derivation of the oral NOAEL. Lack of chronic study data may not be critical in the overall risk assessment evaluation. The commenter recommends that the Office of Science revise the document to justify use of the uncertainty factors of ten (10) and consider using an uncertainty factor of three (3) to account for subchronic-to-chronic.

Response: Both the USEPA and the NJDEP Office of Science use a default uncertainty factor of 10 unless there is specific evidence to indicate that the uncertainty is less than the maximum assumed uncertainty, or unless a specific pharmacokinetic/pharmacodynamic adjustment is applied to reduce the maximum uncertainty for interspecies extrapolation. In such cases an uncertainty factor of 3 (or 1) can be considered *in lieu* of the default of 10. The use of the default uncertainty factor of 10 does not require a specific justification other than the lack of data that can be used to reduce uncertainty. The Office of Science disagrees with the commenter's characterization of the acute and subchronic toxicological database for HCFC-143a as "robust," In contrast, we consider the overall characterization of the level of confidence in the assessment in the draft document as "low" to be appropriate. In our judgement the available toxicological data are minimal and provide little specific evidence that would allow us to support an assumption that any of the key areas of uncertainty addressed by the uncertainty factor adjustments is less than the assumed maximum.

Comment: The Office of Science used an RSC factor of 0.2, meaning that 20% or less of daily exposure to HCFC-143a is attributable to ground water exposure, with the other 80% of daily exposure attributed to sources which have not been described in the document. The commenter recommends that the Office of Science reevaluate the RSC factor used in the derivation of the Interim Specific Criterion of 5,000 µg/L and provide adequate justification for the use of the RSC factor selected, with an explanation of other exposure pathways considered when selecting the RSC factor.

Response: The default RSC of 0.2 is used by both the USEPA and the NJDEP Office of Science unless there is chemical-specific information on sources of exposure that can justify the substitution of a more-specific value. We are unaware of any such information for HCFC-143a, nor has the commenter provided any such information.

Summary of Comments and Responses for the Draft Interim Specific Groundwater Criterion Support Document for 1,1-Dichloro-1-Fluoroethane (HCFC-141b)

Comments of the draft Interim Specific Groundwater Criterion Support Document for 1,1-Dichloro-1-Fluoroethane (HCFC-141b) were received from a single source. The comments from that source are summarized below.

Comment: Consideration should be given to including a modifying factor in the derivation of the oral LOAEL that, with appropriate justification, could raise the oral LOAEL to be higher than 693 mg/kg-day given that no oral absorption data are available for HCFC-141b and absorption efficiency via the oral and inhalation routes is not likely to be identical, especially given that the physical form of HCFC-141b is a gas.

Response: HCFC-141a is not highly reactive, and has limited aqueous solubility. It is, therefore, not expected to have point-of-contact toxicity in the respiratory tract, or specific respiratory tract

toxicity. Rather, as discussed in the draft document, it is well absorbed and distributes systemically. Given these considerations, it is expected that the toxicity HCFC-141b will not be substantially influenced by the route of exposure. The underlying assumption in the commenter's suggestion of an upward adjustment to the oral NOAEL derived from the inhalation NOAEL is that HCFC-141b is likely to be less toxic by the oral route of exposure than by the inhalation route. The commenter, however, provides no scientific rationale to support this suggestion and we are unaware of any evidence to support such an assumption.

Comment: Because of the robust nature of the acute and chronic inhalation studies described in the document, justification can be made that the LOAEL-to-NOAEL uncertainty factor of ten (10) may be overly conservative and an uncertainty factor of three (3) may be more appropriate, especially given that no consideration for the 1:1 route-to-route extrapolation from inhalation to oral exposure has been used in the derivation of the oral reference dose. The commenter recommends that the Office of Science revise the document to justify use of the uncertainty factors of ten (10) and consider using an uncertainty factor of three (3) to account for LOAEL-to-NOAEL.

Response: Both the USEPA and the NJDEP Office of Science use a default uncertainty factor of 10 unless there is specific evidence to indicate that the uncertainty is less than the maximum assumed uncertainty, or unless a specific pharmacokinetic/pharmacodynamic adjustment is applied to reduce the maximum uncertainty for interspecies extrapolation. In such cases an uncertainty factor of 3 (or 1) can be considered in lieu of the default of 10. The use of the default uncertainty factor of 10 does not require a specific justification other than the lack of data that can be used to reduce uncertainty. With respect to the uncertainty factor for the LOAEL-to-NOAEL extrapolation, an uncertainty factor of 3 rather than 10 would be appropriate if, for example, the LOAEL was the only adverse endpoint noted in relevant studies and the corresponding endpoint was of minor or equivocal toxicological significance. In this case, however, the LOAEL is from a reproductive toxicity study for which the adverse endpoint was decreased body weight in the F_1 generation. We do not consider this to be a minor or equivocal endpoint and therefore, do not believe that there is a basis for reducing the uncertainty factor for the LOAEL-to-NOAEL extrapolation from 10 to 3.

Comment: The Office of Science used an RSC factor of 0.2, meaning that 20% or less of daily exposure to HCFC-141b is attributable to ground water exposure, with the other 80% of daily exposure attributed to sources which have not been described in the document. The commenter recommends that the Office of Science reevaluate the RSC factor used in the derivation of the Interim Specific Criterion of 500 µg/L and provide adequate justification for the use of the RSC factor selected, with an explanation of other exposure pathways considered when selecting the RSC factor.

Response: The default RSC of 0.2 is used by both the USEPA and the NJDEP Office of Science unless there is chemical-specific information on sources of exposure that can justify the substitution of a more-specific value. We are unaware of any such information for HCFC-141b, nor has the commenter provided any such information.

Summary of Comments and Responses for the Draft ISGWQC for 1,4-Dioxane

Four commenters submitted comments on the draft Interim Specific Ground Water Criterion (ISGWQC) for 1,4-dioxane.

Question 1: Are you aware of additional data or technical information concerning the toxicology, epidemiology, toxicokinetics, or other topics related to health effects of any of these chemicals that should be considered in the development of the respective interim ground water quality criterion?

Comment: All four commenters mentioned the paper by Dourson et al. (2014) which was published subsequent to the IRIS (2013) assessment of 1,4-dioxane. The draft ISGWQC for 1,4-dioxane is based on the USEPA IRIS (2013) assessment. IRIS (2013) derived a cancer slope factor for this contaminant, based on a linear, non-threshold assumption for liver carcinogenicity. Dourson et al. (2014) conclude that the weight of evidence suggests that 1,4-dioxane causes liver tumors through a mechanism that is secondary to cytotoxicity and regenerative hyperplasia. This conclusion is based primarily on a review of the liver histopathology from one of the chronic oral studies of 1,4-dioxane in mice (NCI, 1978). They suggest that the risk assessment should, therefore, be based on a threshold mode of action for liver tumors caused by 1,4-dioxane.

Response: In summary, the data and explanation provided by Dourson et al. (2014) do not indicate that the non-threshold approach used by EPA IRIS (2013) is inappropriate or that a threshold approach should be used instead.

1,4-dioxane caused multiple tumor types in several drinking water studies in mice and rats. Three chronic rodent studies of 1,4-dioxane in drinking water have been conducted (Kociba et al., 1974; NCI, 1978; Kano et al., 2009). These studies included 3 strains of rats and two strains of mice. In one or more of these studies, 1,4-dioxane caused liver tumors in male and female rats and mice, and nasal cavity, peritoneal, and mammary gland tumors in male and female rats.

The USEPA IRIS (2013) oral cancer assessment for 1,4-dioxane is based on liver tumors in female mice from Kano et al. (2009). This study was chosen because it used more dose groups and lower doses than NCI (1978), and because it reported both hepatic adenomas and carcinomas while Kociba et al. (1974) reported only carcinomas. Liver tumors were the most sensitive

tumor endpoint, and female mice were selected because they were more sensitive to this effect than male mice or either gender of rats.

USEPA IRIS (2013) concluded that the available information does not establish a plausible mode of action for 1,4-dioxane, and that the available data are not sufficient to establish significant biological support for a non-linear, threshold mode of action. Linear, non-threshold, low-dose extrapolation is recommended in the USEPA (2005) cancer guidelines when the mode of action for carcinogenicity is not well understood, as is the case for 1,4-dioxane. Accordingly, IRIS (2013) used a linear, non-threshold, low dose extrapolation approach to develop an oral cancer slope factor for 1,4-dioxane.

Dourson et al. (2014) conducted a pathology review of the liver slides from male and female B6C3F1 mice from the NCI (1978) chronic oral study of 1,4-dioxane. In that study, the dose levels and liver tumor incidence for mice reported by NCI (1978) were as follows:

Males: Control-16%, 720 mg/kg/day-38%, 830 mg/kg/day-60%.
Females: Control-0%, 380 mg/kg/day-44%, 860 mg/kg/day-95%.

The goal of the Dourson et al. review was to determine if non-neoplastic lesions in the liver could be used to understand the mode of action for the liver tumors. Dourson et al. (2014) state that, at the time that the NCI (1978) study was conducted, only the most severe response seen on a slide was recorded, so that if a tumor was observed, non-neoplastic changes on the same slide would not have been noted. Non-neoplastic changes evaluated by Dourson et al. (2014) include glycogen depletion, hypertrophy, necrosis, inflammation, and Kupffer cell hyperplasia. Based on their interpretation of the dose-response for these non-neoplastic effects, Dourson et al. (2014) suggest that these events preceded and were causative to tumor formation. In male mice, a higher incidence and/or greater severity for all of these effects were observed in both the high and low dose group as compared to controls. However, in female mice, the incidence and/or severity of glycogen depletion, necrosis, inflammation, and Kupffer cell hyperplasia was similar or greater in controls as compared to the low dose group, and was increased in the high dose group as compared to controls in the high dose group.

Dourson et al. (2014) suggest that 1,4-dioxane causes liver tumors in rats and mice through a pathway involving cytotoxicity (as indicated by hypertrophy and necrosis) followed by regenerative hyperplasia, and that a threshold approach is therefore appropriate for risk assessment for this compound. However, this conclusion is not supported by the data in female mice. In female mice, the incidence of liver tumors in the control and low dose groups were 0 and 44% respectively, while the incidence of necrosis and other non-neoplastic effects is similar or lower in the low dose group as compared to the controls. These data suggest that necrosis is not part of the sequence of events leading to tumor formation in the low dose female mice.

Dourson et al. (2014) acknowledge this issue, and state that the non-neoplastic effects were more apparent in males than females, and that this may be due to the fact that the low dose in females was about half of the low dose in males. However, this is not a logical explanation since the incidence of liver tumors in low dose females (44%, as compared to 0% in controls) is greater than in low dose males (38%, as compared to 16% in controls) at a dose almost 2-fold higher.

Dourson et al. (2014) also state that the incidence of non-neoplastic changes in the female controls may have been due to a viral infection that "was known to occur in **all mice** at the time of the bioassay." This explanation is not logical, since the control females were not stated to be specifically infected with the virus, as compared with other groups of male and female mice. Furthermore, the statement that a virus occurred in all mice at the time of the bioassay is attributed to E.E. McConnell, one of the authors of Dourson et al. (2014) who also conducted the pathology review. However, no citation is provided related to the presence of the viral infection, and a possible or known viral infection is not mentioned in either NCI (1978) or the pathology review report by Dr. McConnell. Most importantly, if the pathway hypothesized by Dourson et al. (2014), in fact, resulted in tumors, then the presence of the elements of this pathway in control females, with incidence of necrosis and inflammation greater than in the low dose group, would also have been expected, regardless of its etiology, to result in tumors. The absence of tumors in the control females is thus, inconsistent with the hypothesized link between the non-neoplastic changes observed in both control and treated mice and the observed tumors.

Additionally, it should be noted that female mouse liver tumors from Kano et al. (2009), not NCI (1978) study, were used as the basis for the oral slope factor. In this study, Crj:BDF1 mice were used. The doses and liver tumor incidences in female mice were:

Control-10%; 66 mg/kg/day-70%; 278 mg/kg/day-82%; 964 mg/kg/day-92%.

Finally, Dourson et al. (2014) state that the lower incidence of non-neoplastic changes in the female mice, as compared to the male mice, in NCI (1978) may be due to the fact that the low dose in females was lower (about half) than the low dose in males. Although non-neoplastic changes such as necrosis are not reported by Kano et al. (2009), it should be noted that the low dose in this study (66 mg/kg/day) was almost 6-fold lower than the low dose in NCI (1978) (380 mg/kg/day). However, the tumor incidence in the low dose group (70% compared to 10% in controls) in Kano et al. (2009) is higher than at the much higher dose (380 mg/kg/day) in NCI (1978). When considered as a whole, these findings do not support the conclusions of Dourson et al. (2014) that non-neoplastic changes both occur more frequently at higher doses and are necessary precursors to tumor formation.

In conclusion, the data and explanation provided by Dourson et al. (2014) do not establish a firm or unique link to the proposed MOA of cytotoxicity followed by regenerative hyperplasia, and does not indicate that a threshold approach is appropriate for risk assessment for this compound. As such, the information provided by Dourson et al. (2014) does not invalidate the conclusion

made by USEPA IRIS (2013) that the available information does not establish a plausible mode of action for 1,4-dioxane, and that the available data are not sufficient to establish significant biological support for a non-linear (threshold) mode of action. For these reasons, the approach used by USEPA IRIS (2013) which uses a linear low dose extrapolation to develop an oral cancer slope factor for 1,4-dioxane is appropriate.

Comment: Two commenters discussed *in vitro* assay data for 1,4-dioxane from the Tox 21 (Toxicology in the 21st Century) program and other publications. One commenter stated that these data eliminate some receptor-mediated effects, as well as DNA reactivity and induction of genotoxic stress, as part of the cancer MOA for this compound. This commenter also stated that cytotoxicity occurred in some in vitro assays at very high (0.3 - 20%) 1,4-dioxane concentrations. This commenter states that because the assays were conducted without metabolic activation, liver toxicity due to metabolites is not ruled out. In conclusion, the commenter states that further studies are needed to arrive at a conclusive MOA for liver cancer from 1,4-dioxane.

Response: The *in vitro* data presented by the commenters suggest that 1,4-dioxane does not act through certain modes of action. As mentioned by one of the commenters, these data do not address the mode(s) of action of the metabolites of 1,4-dioxane and also do not establish the mode of action by which 1,4-dioxane is carcinogenic. As stated by the commenter, further research is needed to establish the MOA for 1,4-dioxane. For these reasons, these data do not indicate that the non-threshold approach used by EPA IRIS (2013) is not appropriate and that a threshold approach should be used instead.

Comment: One commenter stated that the 2010 USEPA oral assessment that was referenced in the supporting documentation for the draft ISGWQC was updated in September 2013 and that the 2013 update includes studies that were not considered when the draft ISGWQC for 1,4-dioxane was developed.

Response: The updated 2013 IRIS Toxicological Review states that most of the new information relates to inhalation exposure to 1,4-dioxane and that the few comments relating to oral exposure that were addressed in the update did not impact the final conclusions of the oral assessment presented in the 2010 document.

Comment: Four commenters cited conclusions by other agencies and researchers from prior to 2013 related to the mode of action of 1,4-dioxane. These include Environment Canada (2010), National Industrial Chemicals Notification and Assessment Scheme (Australia, 1998), Stickney et al. (2003), Health Council of the Netherlands (2004), and WHO (2005). It is stated that these documents conclude that 1,4-dioxane acts through a non-linear MOA and/or that it is non-genotoxic or that it is weakly genotoxic only at high doses that also cause toxicity.

Response: All of these documents precede the IRIS (2013) assessment, and EPA considered the studies from these evaluations. Because the draft ISGWQC is based on the EPA IRIS assessment, these documents were not evaluated in detail in developing this response to comments. However, it should be noted that, while a commenter states that WHO (2005) presents an approach based on a threshold for toxicity for regulation of 1,4-dioxane, the document actually presents risk-based water values based on both threshold and non-threshold (linear low-dose extrapolation) approaches.

Question 2: Are any of the supporting documents factually inaccurate, e.g., are the data sources incorrectly cited; are the calculations incorrect?

Comment: One commenter suggested that the defaults recommended by the EPA Office of Solid Waste and Emergency Response (OSWER) for daily water consumption (2.5 L per day) and adult body weight (80 kg) be used instead of 2 L/day and 70 kg.

Response: The values used for daily water consumption and body weight are the default values provided in the NJ Ground Water Quality Standards regulations and are consistent with the values used by EPA Office of Water for its drinking water Maximum Contaminant Level Goals and Lifetime Health Advisories. Based on the ratios of the assumed values for daily water consumption to assumed body weight, the two sets of parameters result in very similar estimates of daily water consumption on a body weight basis, 0.031 L/kg/day for the OSWER parameters and 0.029 L/kg/day for the parameters used to develop the ISGWQC.

Comment: One commenter stated that the IRIS (2013) slope factor used as the basis for the ISGWQC does not accurately reflect the potential human risk of 1,4-dioxane in water. The conclusions of Dourson et al. (2014), discussed in the response to Charge Question 1 above, were again presented. The commenter recommended a drinking water value of 350 µg/L derived by Dourson et al. (2014) using a Reference Dose derived based on a threshold approach.

Response: As discussed in the response to Charge Question 1 above, the data and explanation provided by Dourson et al. (2014) do not indicate that the non-threshold approach based on a slope factor used by EPA IRIS (2013) is inappropriate and that a threshold approach based on a Reference Dose should be used instead.

Question 3: Is the choice of study and toxicological endpoint used as the quantitative basis for development of each criterion appropriate?

Comment: Three commenters reiterated that the ISGWQC should be based on a threshold approach, as recommended by Dourson et al. (2014), instead of the non-threshold approach used by IRIS (2013). One of these commenters said that the study and toxicological endpoint used as the basis for the ISGWQC was appropriate but that the threshold MOA and revised exposure

parameters (discussed in Charge Question 2, above) should be used. Another of these commenters recommended that a Reference Dose derived by Dourson et al. (2014) based on Benchmark Dose modeling of non-neoplastic effect (liver and kidney degeneration) in Sherman rats exposed to 1,4-dioxane in drinking water be used.

Response: As discussed in the response to Charge Question 1 above, the data and explanation provided by Dourson et al. (2014) do not indicate that the non-threshold approach based on a slope factor used by EPA IRIS (2013) is inappropriate and that a threshold approach based on a Reference Dose should be used instead.

Question 4: Have the key uncertainties in each 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 any of these documents?

Comment: One commenter said that it is not clear where the uncertainties associated with the derivation of the ISGWQC for 1,4-dioxane are discussed.

Response: The draft ISGWQC is based on the risk assessment presented in EPA IRIS (2013). Uncertainties related to the risk assessment are discussed in Section 5.5 of EPA IRIS (2013).

Comment: Three commenters stated that lack of understanding of the mode of action of 1,4-dioxane is a key uncertainty that was not understood when the draft ISGWQC was developed. The commenters stated that Dourson et al. (2014) has shown that 1,4-dioxane causes liver tumors through a threshold mode of action. The commenters referred to their comments on this issue in response to other charge questions (above and below).

Response: As discussed in the response to Charge Question 1 above, the data and explanation provided by Dourson et al. (2014) do not indicate that the non-threshold approach based on a slope factor used by EPA IRIS (2013) is inappropriate and that a threshold approach based on a Reference Dose should be used instead.

Question 5: Do you agree with the Department's conclusion to support the IRIS value (or to modify the IRIS value by an additional uncertainty factor of 'x' to account for 'y'), where used to derive the interim criterion?

Comment: Three commenters stated that they do not agree with the Department's conclusion to support the IRIS risk assessment of 1,4-dioxane. They reiterated their support for the conclusions of Dourson (2014) that the mode of action for this chemical indicates that a threshold approach should be used. Two commenters referred to their comments on this issue in response to other charge questions. One commenter recommended that the Reference Dose developed by Dourson et al. (2014) be used as the basis for the ISGWQC, and another

commenter suggested that an additional uncertainty factor of 10 to account for carcinogenic effects when a slope factor is not applicable be applied to the Reference Dose derived by Dourson et al. (2014).

Response: As discussed in the response to Charge Question 1 above, the data and explanation provided by Dourson et al. (2014) do not indicate that the non-threshold approach based on a slope factor used by EPA IRIS (2013) is inappropriate and that a threshold approach based on a Reference Dose should be used instead.

Other Comments not related to the Focus Questions:

Comment: Moreover, it is relevant to this process to point to the "Common Sense Principles" established by Governor Christie in Executive Order No. 2 (EO #2) issued on January 20, 2010. Among the principles outlined in the Order were the following:

- Engage in the "advance notice of rules" by soliciting the advice and views of knowledgeable persons from outside of New Jersey State government, including the private sector and academia, in advance of any rulemaking…
- Employ the use of cost/benefit analyses, as well as scientific and economic research from other jurisdictions, including but not limited to the federal government when conducting an economic impact analysis on a proposed rule.
- Detail and justify every instance where a proposed rule exceeds the requirements of federal law or regulation. State agencies shall, when promulgating proposed rules, not exceed the requirements of federal law except when required by State statute or in such circumstances where exceeding the requirements of federal law or regulation is necessary in order to achieve a New Jersey specific public policy goal.

Interim standards, while more easily revised by the NJDEP, have the same impact once published as a standard adopted through formal rulemaking. As such, SRIN and CCNJ believe strongly that the NJDEP, to date, has failed to give appropriate consideration to EO #2 with respect to this IGGWQC process.

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 the adverse impacts of these chemicals to warrant the Department's creation of ISGWQC. While public

comment is not a requirement for the establishment of an ISGWQC, the Department elicited comments from the public in 2015. The Department considers this public mechanism consistent with the principles of Executive Order No. 2.